

# **Developing a Value Framework for Genetic Diagnosis: Part I**

## **A Systematic Review of Outcomes Hierarchies and Measurement Approaches**

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**Prepared for:**

American College of Medical Genetics (ACMG)  
*ACMG Ad Hoc* Committee on the Value of Genetic Diagnosis

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the American College of Medical Genetics.

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## Commonly Used Acronyms and Abbreviations

ACC/AHA	American College of Cardiology/American Heart Association
ACMG	American College of Medical Genetics
AHRQ	Agency for Healthcare Research and Quality
CAD	Coronary artery disease
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CGS	Clinical genetic services
CUA	Cost-utility analysis
EMR	Electronic medical records
EU	European Union
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
HbA <sub>1c</sub>	Hemoglobin A <sub>1c</sub>
HRQL	Health-related quality of life
IOM	Institute of Medicine
NICE	United Kingdom (UK) National Institute for Health and Clinical Excellence
NIH	National Institutes of Health (DHHS)
NQMC	National Quality Measures Clearinghouse
PROs	Patient-reported outcomes
QA	Quality assurance
QALY	Quality adjusted life year
QI	Quality improvement
QOF	UK Quality Outcomes Framework
QOL	Quality of life
QSR	Qualitative Systematic Review
RW	“real world”, as in “RW data”
SER	Systematic evidence review
TEP	Technical Expert Panel
UK NHS	UK National Health Service
US	United States

## EXECUTIVE SUMMARY

### Introduction

This qualitative systematic review was commissioned by the American College of Medical Genetics and the ACMG Ad Hoc Committee on the Value of Genetic Diagnosis. The Committee's charge was to "critically examine the value that making a specific genetic diagnosis brings to the patient, family and health care system". The type of review, methods, and key questions were designed by the Committee members in concert with two external consultants experienced in structured evidence review. The Ad Hoc Committee served as the Technical Evaluation Panel (TEP) that provided comment and guidance as well as oversight of the process. The Chair of the Committee / TEP is Marc Williams, MD, FAAP, FACMG. Linda A Bradley, PhD, FACMG and Glenn E. Palomaki, PhD performed the review. Funding for the review was provided by the ACMG Foundation through a contract with Women & Infants Hospital of Rhode Island.

### Methods

The initial scope of this review was modified during article selection and review to fit available resources, by deferring review of KQ 6 on costs and economics (the denominator of value as defined by quality/outcomes related to costs). There was consensus that the most productive approach and appropriate order of review would be to examine quality/outcomes first and costs/economics second. The refocused report is organized around key questions (KQ) 1 through 5 and a review framework established in consultation with the TEP. The first, or over-arching question, KQ1, asks whether there is an existing framework for examining value that could be applied to genetic diagnoses. The remaining KQs were aimed at establishing a potential 'chain of evidence' to provide components that could be used to build such an outcomes framework. KQ 2 and KQ 3 addressed background, concepts and definitions that would be relevant to consideration of the value numerator, outcomes. KQ 4 addressed health outcomes or clinical utility, and KQ 5 other outcomes or personal utility, from multiple perspectives when possible. The methods used to gather information included: structured electronic searches of the published literature, review of reference lists of selected articles, and other searches of grey literature (e.g., web sites, policy reports, government white papers). Relevant data was abstracted and organized by key question and analyzed using appropriate qualitative methods. Each section devoted to a KQ begins with a general introduction, review of relevant data sources and findings, a summary paragraph, an assessment of the quality of individual studies (*Good, Fair, Poor*) and the overall quality level of findings for that KQ (*Inadequate, Adequate, Convincing*).

### Results for Key Questions (KQ)

Overall, 81 peer-reviewed publications, 16 web-based document and one book chapter from initial searches were reviewed and abstracted.

KQ1: "Can an evidence-based and/or validated framework be identified that can be used to examine the value of making a specific genetic diagnosis from the perspective of the patient,

*family, health care providers, payers, health care sector, public health and society?"* No single source was identified that provided an evidence-based and/or validated framework satisfying the overarching question. This was not an unexpected finding, as many medical specialties are struggling with the issue of measuring value, particularly in the context of the US health care system. Subsequent work by the Committee will be to determine whether the other KQs produced a chain of evidence that included information, methods, outcomes hierarchies or models that can be applied and validated for use in genetic diagnoses.

KQ2: *What can be learned from existing value frameworks in health care?* Eighteen relevant articles/documents (six rated *Good*) were identified. Several sources defined 'value' in the health care setting, and in general these were quite consistent. All considered it a ratio of some measure of health benefit, quality or outcomes and financial resources (dollars, costs, money spent). Components of value identified also included measures of process (e.g., patient-provider interaction, care coordination) and structure (e.g., medical facilities and staff that support care), access (i.e., attainment of timely and appropriate health care) and related innovations. Published and grey literature sources provided outcome hierarchies or models that evolved from 1966 to 2010. Later hierarchies and models included wider ranges of health and personal outcomes, demonstrated more standardized language, and sometimes addressed validated measurement tools. One model proposed for measurement of value focused on outcomes and did not address costs.

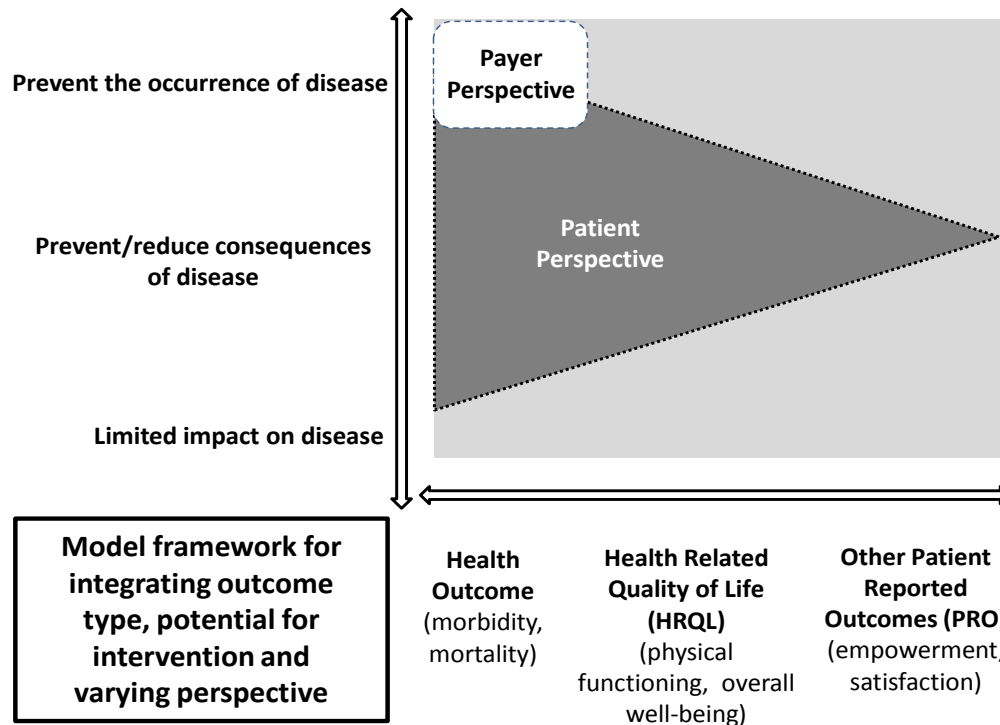
KQ3: *How should genetic diagnosis be defined / what are the components of genetic diagnosis)?* The TEP recommended a focus on "classical" genetic diagnoses. Thirty-one articles/documents (13 rated *Good*) were identified, and common themes included: the comprehensive scope of clinical, education and supportive services; the added value of effective communication to patients and family members; and the need to make the case for the value of genetic services to payer and policy-makers.

KQ4: *What are specific health outcomes and how does a diagnosis contribute to improved short- and long-term outcomes for a) patients, b) family members and c) health care delivery systems and/or public health programs?* Sixty-seven articles/documents (32 rated *Good*) were considered relevant. Six outcome hierarchies were identified, but only two focused on health outcomes. Hierarchies included health outcomes, intermediate outcomes, health-related outcomes (e.g., quality of life), patient reported outcomes, and process and structure outcomes. A review of clinical genetic outcome studies reported that 52 of 55 did not report on health outcomes, revealing the current focus on process measures. Some specialties (e.g., Cardiology, Orthopedics) are leading the way in outcomes research and development and validation of outcome measures. A key difference for many genetic diagnoses was that effective interventions that would provide short- or long-term health improvements were not available. Particularly in such instances, other outcome measures (e.g., quality of life, access to services, support) may be of more relevance to patients and health care providers.

**KQ5:** *What specific outcomes have been proposed that provide other utility to the individual, family members, health care delivery systems or public health, and how does establishing a genetic diagnosis contribute to improvement in these outcome?* Thirty-one articles/documents (13 rated *Good*) were relevant to this key question. Rather than the objective measures of short- and long-term health outcomes covered in KQ4, KQ5 focuses on more subjective measures related to patient-reported outcomes (PROs) and personal utility. These include health-related quality of life (HRQL), with measureable domains such as physical functioning, emotional functioning, vitality and overall well-being. Also included are domains such as patient satisfaction and empowerment. Several validated tools exist for assessing HRQL or PRO and multiple publications have examined scenarios involving a genetic diagnosis. However, little or no information exists on how health plans, payers and other stakeholders view these more subjective measures.

## **Conclusions**

No existing value framework was identified in the published and grey literature that addressed both the broad range of clinical scenarios, perspectives and measureable outcomes related to genetic diagnoses, and the costs (e.g., selected cost measures, data sources and collection approaches, economic models, metrics of economic impact and value). Another key dimension of an outcomes hierarchy or framework is the perspectives that health care providers, patients/families, health systems, payers, public health and society bring to the consideration of levels of interventions and types of outcomes measured. A preliminary framework for considering outcomes of genetic diagnoses in the context of the potential for clinical intervention is presented. Another over-arching structure the Committee discussed for developing a flexible outcomes framework is demonstrated in Figure 1 below. In addition to the type of outcome (a continuum shown on the x-axis), the possible level of intervention for the disease being diagnosed (y-axis) is also be considered. Within this two-dimensional space, various stakeholders perspectives could be specified. Subsequent development or adoption of a value framework for genetic diagnoses will require integration of outcomes organized as hierarchies / frameworks and/or models, as well as frameworks and/or models addressing costs and economics (Part II).



**Figure 1. Proposed overarching structure for a model outcome framework**

### Research Agenda

- Seek resources to support Part II, a systematic evidence review that minimally addresses, from multiple perspectives, KQ 6 from this review: *What approaches have been used to measure the economic impact of establishing a genetic (or other) diagnosis?* The review would include the variables that will be considered in determining costs (e.g., costs to the patient versus the health care system and/or society; costs for a single encounter or “episode of care” versus multi-specialty and/or long-term care), a review of relevant economic models and examples of economic analyses related to genetic diagnoses. In addition, it would address the combination of outcomes and costs (defined as values) using two approaches, examples with values as the outcome identified by structured literature review and describing existing models for deriving value.
- Based on the current evidence review, consider the growing importance of patient and family member’s perspectives on outcomes of interest in developing outcomes frameworks or hierarchies.
- Once outcomes frameworks or hierarchies are established, design specific projects for validation in well-defined and broadly applicable clinical scenarios.
- Develop, validate and pilot selected outcome measures for feasibility, reliability and resources needed for collection.



- Determine how genetic disease-specific research findings on outcomes from individual primary studies already available in the literature could be effectively collected and used within outcomes frameworks and hierarchies.
- Identify existing sources of data in which both measures of outcome and costs for a genetic diagnosis might both be available.
- Establish communication with select specialties that are already engaged in developing relevant outcomes and process measures or hierarchies and/or determining health-related value, in order to collaborate with them on projects and/or consult with them about common experiences.

## INTRODUCTION

### Background and Context

#### Quality and Value in Health Care

There has been a strong national policy interest in health services research to determine the quality of health care for more than three decades. In 1988, legislative policy makers faced with rising costs of health care noted that:

*“..their concern was best embodied in the word **value**”, as Congress looked for ways to obtain more “..value for the public dollars spent on health care”.*

Legislation was introduced that year to promote value in health care by increasing funding for assessment of outcomes of health care practices.<sup>1</sup> The goals were to improve quality and address increasing costs through systematic development of evidence-based “physician-generated practice guidelines” on the effectiveness and appropriate use of health services.<sup>1</sup>

In 1990, the Institute of Medicine (IOM) defined *quality* in health care as:

*“..the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.”<sup>2,3</sup>*

This definition was reaffirmed in 2001 in a report from the IOM Committee on Quality of Health Care entitled *Crossing the Quality Chasm: A new health system for the 21<sup>st</sup> century*.<sup>4</sup> The American College of Medical Quality (ACMQ) followed the IOM’s lead, but modified the definition of “Medical Quality” (Policy 1) as:

*“..the degree to which health care systems, services and supplies for individuals and populations increase the likelihood for positive health outcomes and are consistent with current professional knowledge.” (<http://www.acmq.org/policies/policies1and2.pdf>)*

However, the meaning of the word *quality* has changed over time, with use in different contexts, and based on varying perspectives of health care stakeholders. In recent literature, ‘quality’ was largely related to adherence to evidence-based clinical guidelines and use of approved ‘quality measures’ for health care processes and health outcomes<sup>5</sup> (e.g., American College of Cardiology/American Heart Association<sup>6,7</sup>, National Quality Measures Clearinghouse<sup>8</sup>, Quality and Outcomes Framework<sup>9</sup>). However, some variability remained with regard to the characterization of ‘quality’.<sup>10</sup>

#### Quality Improvement

Other initiatives have sought to “transform” health care through the process of quality improvement. Batalden and Davidoff<sup>11</sup> define *quality improvement* (QI) as:

*“..the combined and unceasing efforts of everyone – healthcare professionals, patients and their families, researchers, payers, planners and educators – to make the changes that will lead to better patient outcomes (health), better system performance (care) and better professional development (learning).”*

Healthcare organizations worldwide are being encouraged or required to initiate and/or participate in QI programs that use prospective and retrospective review to collect data, define outcomes of interest and develop or promote evidence-based practice guidelines.<sup>11-13</sup> The QI process differs from research in that its purpose is to change the performance of people, rather than provide new generalizable knowledge.<sup>14</sup> Improvement is context dependent, and must be continually responsive to feedback. Although some QI programs in disease-specific settings have reported measureable improvement, these programs are resource intensive.<sup>12</sup> Implementing QI programs in specialist services like clinical genetics has been particularly challenging, based on the complexity of the services offered and difficulty in obtaining measurable and reliable outcome data on rare disorders.<sup>15</sup> Consequently, literature on QI in clinical genetics was limited. Here again, the definitions of 'quality' and 'QI' can be controversial, based on views of different stakeholders.

### **Purpose and Scope of the Review**

This qualitative systematic review was commissioned by the American College of Medical Genetics Foundation for the American College of Medical Genetics (ACMG) Ad Hoc Committee on the Value of Genetic Diagnosis (contracted May 1, 2011). The ACMG Mission Statement is to "Improve Health Through Medical Genetics", and one of five stated goals is to "Maintain structure and integrity of ACMG and its value to members and the public".

However, quantifying the value genetics professionals bring to healthcare, or even the value of specific genetic diagnoses, has proved challenging. In late 2010, the ACMG Board of Directors established the *ACMG Ad Hoc Committee on the Value of Genetic Diagnosis* (the Committee), Chaired by Dr. Marc Williams. The Committee's charge was to "...critically examine the value that making a specific genetic diagnosis brings to the patient, family and health care system."

Specific questions developed by the Committee in initial deliberations included<sup>16</sup>:

1. What are the components of a genetic diagnosis (*i.e.*, roles of clinical criteria and genetic testing)?
2. How does establishing a clinical diagnosis contribute to the management of an affected individual?
3. How does establishing a clinical diagnosis contribute to the care of the family of an affected individual?
4. What is the economic impact of establishing a diagnosis?
5. Is there other value that accrues from establishing a diagnosis?

The Committee's objectives were to frame key questions based on the above issues, assess literature addressing these key questions, and, ultimately, present proposed next steps to the ACMG Board of Directors. In March, 2011, the Committee presented findings on their deliberations, and sought audience participation and feedback at the Quality Improvement SIG *Forum on Value in Health Care* at the ACMG Annual Meeting. Presentations were made based on the 2010 New England Journal of Medicine article by Dr. Michael Porter, entitled "*What is*

*Value in Health Care?*<sup>17</sup> The information included Porter's definition of "value" and Health Outcome Measures Hierarchy, as well as the related Health Care Delivery Value Chain.<sup>18</sup> Dr. Williams presented his application of the Porter Health Outcome Measures Hierarchy to the example of testing for Lynch syndrome in individuals with newly diagnosed colorectal cancer (CRC), with the primary aim of preventing CRC-related morbidity and mortality in their family members.

Two evidence review options were proposed and discussed: 1) select a specific test(s) and clinical scenario(s) and conduct a systematic review of available information on health outcomes (quality) and costs using the Porter Health Outcomes Measures Hierarchy; or 2) conduct a qualitative systematic review of existing proposed approaches and frameworks for measuring value and its components. The second alternative was selected by the Committee and approved by the ACMG Board of Directors.

It was decided that the Committee would serve as the Technical Expert Panel (TEP) for the review, with the addition of a consultant in Health Economics. The TEP would select and invite 3 to 5 outside experts to review the draft report. In several discussions of review scope, the TEP considered two important decisions:

- First was what definition of 'genetic diagnosis' would be used for the review. It was decided that the review should focus on a 'classic' definition of genetic diagnosis (e.g., diagnosis of disorders due to mutations in single genes or copy number variants, newborn screening), rather than prediction or diagnosis of common complex disorders or pharmacogenomic testing for variable response to medication. It was noted that there could be exceptions made when providing examples in the review.
- Second was whether the review would consider the broad range of process measures that have been described in the literature. Process measures evaluate interactions between healthcare providers and patients, and assess the quality of a range of actions and functions of routine health care related to patients (e.g., appointment scheduling, care coordination). It was noted that some process measures could be integral in achieving better patient outcomes (or preventing them) and could impact costs. In 2009, Zellerino et al.<sup>19</sup> identified a wide range of process measures specific to genetic services. While acknowledging that some articles on 'value' may include process measures, the TEP preferred to focus on patient health outcomes, with exceptions for select process measures that are directly linked to health outcomes (e.g., compliance).

In summary, this qualitative systematic review (QSR) compiled available information focused on the topics of quality and value in health care, with a focus on clinical genetics. The overarching question for the summary and qualitative analysis of the relevant published and grey literature was:

*Can an evidence-based and/or validated framework be identified that can be used to examine the value of making a specific genetic diagnosis, from the perspective of the patient, family, health care providers, payers, health care sector, public health and society?*

The aims were to: 1) develop clear working definitions; 2) characterize relationships between quality, value and other related concepts; and 3) consider how measurement of value may relate to, and potentially stimulate, QI and health services research.

- One component of QI, professional development (education), was not addressed in this review.
- Available resources did not allow the scope of the review to include the wide range of specific outcomes of genetic diagnoses reported in publications of primary studies.

Finally, this review described work in progress, as the concepts of quality, quality improvement and value continue to evolve.

## METHODS

This report presents a “qualitative systematic review” (QSR) of peer-reviewed publications and grey literature relevant to the overarching question.<sup>20,21</sup> Qualitative approaches can be useful in a preliminary stage of research, helping to define the dimensions that quantitative studies will later aim to measure, and to use knowledge gained on perspectives to suggest effective ways of communicating with stakeholders (e.g., patients and their families, health care providers and payers, public health, society).<sup>22</sup> Compared to the rigorous standardized approach of the quantitative systematic evidence reviews (SERs) with which many of us are more familiar, methods for QSR can be somewhat less well defined (or even controversial). Consequently, transparency was important. Like SERs, QSR methods included developing a review framework and key questions, as well as a plan for data collection and analysis. As with all reviews, clear exposition of methods was important to allow the reader to judge if the interpretation and conclusions were adequately supported by the data.<sup>23</sup>

Results in qualitative reviews are more often referred to as “findings”, acknowledging the importance of context and perspective in their generation, and the reporting of information from sources other than research studies.<sup>24,25</sup> This knowledge can fall into four overarching categories: 1) qualitative research on personal perceptions, beliefs, attitudes; 2) qualitative focus on general evidence, such as the organizational, political and social perspectives on an issue, and may involve the study of policy analyses or decision-making (e.g., consensus statements); 3) quantitative research using epidemiological designs to develop scientific evidence; 4) quantitative research on personal beliefs or attitudes (e.g., quality of life scales).<sup>25</sup> Searches for this review were likely to identify articles/documents that fell mainly in knowledge categories 1 and 2, and possibly in category 4.

Document analysis (category 2) was likely to have a larger than usual role in this review. Document analysis was simply a systematic procedure for reviewing both printed and electronic (e.g., web-based) material, such as meeting summaries, background papers, organizational reports, survey data or public records. Document analysis provided a broad range of time and topic coverage and “non-reactive” data; that is the data are not affected by the research process as qualitative study data can be.<sup>26</sup> However, it is important to keep in mind that such documents could show bias based on incomplete ascertainment or as a reflection of the writers’ perspective or ‘agenda’.

### Key Questions and Review Framework

The key questions (Table 1) and review framework (Figure B1, Appendix B) were established in consultation with the TEP to frame the content of the review. The overarching question asks whether there is an existing framework for measuring value as outcomes related to costs that could be applied to genetic diagnoses. If such a framework was not found, the remaining key questions were intended to identify the information needed to define each of the potential

**Table 1. Clinical Validation of LDTs Project - Evidence Review Key Questions**

<p><b>KQ1. Overarching Question:</b> <i>Can an evidence-based and/or validated framework be identified that can be used to examine the value of making a specific genetic diagnosis, from the perspective of the patient, family, health care providers, payers, health care sector, public health and society?</i></p>
<p><b>KQ2.</b> What can be learned from existing value frameworks in health care?</p> <ul style="list-style-type: none"> <li>a. How has value been defined in health care?</li> <li>b. What are proposed components of value?</li> </ul>
<p><b>KQ3.</b> How should genetic diagnosis be defined? What are the components of genetic (or other) diagnoses (e.g., clinical criteria, testing, family history, intervention / therapy)?</p>
<p><b>KQ4.</b> How does establishing a genetic (or other) diagnosis in an individual impact the balance of benefits and harms related to short- and long-term health outcomes?</p> <ul style="list-style-type: none"> <li>a. What are specific health outcomes of interest to the individual patient? How does establishing a genetic (or other) diagnosis contribute to improved short- and long-term health outcomes of patients?</li> <li>b. What are specific health outcomes of interest to patient’s family members? How does establishing a genetic (or other) diagnosis contribute to improved short- and long-term health outcomes of family members?</li> <li>c. What are specific health outcomes of interest to health care providers, payers, health care sector, public health and society? How does establishing a genetic (or other) diagnosis contribute to measurable improvement in short- and long-term health outcomes from these perspectives?</li> </ul>
<p><b>KQ5.</b> What specific outcomes have been proposed that provide other utility (e.g., personal utility) to the individual, family members, health care providers, payers, health care sector, public health and society? How does establishing a genetic (or other) diagnosis contribute to improvement in these outcomes?</p>
<p><b>KQ6.</b> What approaches have been used to measure the economic impact of establishing a genetic (or other) diagnosis? Each question on economic analyses will be addressed from multiple perspectives: patients, family members, health care providers, payers, health care sector, public health and society. <b>[Now Part II.]</b></p> <ul style="list-style-type: none"> <li>a. Describe the variables that will be considered in determining costs (e.g., costs to the patient versus the health care system and/or society; costs for a single encounter or “episode of care” versus multi-specialty and/or long-term care).</li> <li>b. What economic models might be / have been used as part of economic analyses of genetic diagnosis / genetic services?</li> <li>c. What metrics might be / have been used to measure the economic impact of genetic diagnosis / genetic services (e.g., QALYs, willingness to pay, direct costs).</li> </ul>

components (e.g., quality / outcomes, costs) that could be used to construct such a framework.

Note that KQ 2 addressed the general context of health care, not just clinical genetics. In addition, KQs 3-5 included reference to “.genetic (or other) diagnosis”. This allowed broadening of the scope to other medical specialties in areas where specific information for clinical genetics was limited or not available. Such information could be directly applicable to the objectives of this project, or provide examples of relevant approaches.

### **Search Strategy**

Electronic searches of the English language published (MEDLINE®, ISI Web of Knowledge) and grey literature (e.g., Google searches, government and policy web sites) were conducted for the time period January 1, 1990 to September 28, 2011. Searches aimed to identify resources that addressed the key questions (e.g., value in health care, health-related outcomes, outcomes hierarchies, outcomes assessment), either specifically for genetic diagnosis, for other medical specialties, or for health care in general (Review and selection flow diagram; Table B1, Appendix B). The more classic “fixed and linear” search strategy (e.g., one large complex search) can be less productive for qualitative literature, especially in the context of a topic as broad as “value in health care”.<sup>27</sup> Review of references in bibliographies of included materials is effective, as is the “berrypicking model”.<sup>27</sup> Using this model, the reviewer does not rely on a complex query and single retrieval, but uses key identified information to stage multiple searches.

Identified article/document citations were excluded by review of titles for relevance; when relevance was likely or not clear, abstracts were reviewed. If abstracts were not available or relevance remained unclear based on the abstract (or summary), full articles or documents were reviewed. See Table B2 (Appendix B) for general and key question-specific inclusion and exclusion criteria. Hand searching for other relevant citations was done in bibliographies of identified articles.

Grey literature (e.g., policy reports, government white papers, committee opinions or consensus meeting summaries not published in a peer-reviewed journal) was identified through electronic search engines (e.g., Google, LexisNexis), hand searching of referenced materials and web sites, as well as review of relevant US and international websites (listed in Table B3, Appendix B).

### **Change in the Scope of the Review**

During the process of search, selection and review, increasing awareness of specific limitations in resources necessitated reconsideration of the scope of this review. Based on review planning with the Committee, it was clear that documenting the value of a genetic diagnosis would require defining and collecting information on two key value components, outcome(s) of interest and associated costs. Initial estimates of the numbers of abstracts for the outcomes component were about 1,500.



An initial Medline search of economic analyses available in the area of genetic diagnoses focused on review articles on genetic diseases and tests (e.g., MeSH terms “genetic testing/economics”, “genetic services/economics”). Of the 127 articles from a preliminary search, most addressed a single genetic disorder, but there were three systematic reviews in the areas of genetic screening<sup>28</sup> and diagnosis.<sup>29,30</sup> The 95 reports meeting inclusion criteria addressed cost-effectiveness or cost utility analyses (80%), as well as value thresholds and value-based pricing. Review of information sought in Key Question 6 (e.g., costs selected, data sources and collection approaches, economic models, metrics of economic impact) would take resources comparable to the other five KQs, as well as expertise in the areas of health economics, clinical genetics and behavioral economics.

In summary, the review of Key Question 6, related to identifying and analyzing relevant costs, cost metrics, data sources and collection methods, economic models, and selected clinical genetics economic examples, as well as value metrics and interpretation of value, would be left to another time and process (i.e., Part II). Information identified in the initial searches that related to general concepts of value, value definitions, and value components was collected and reported, along with the information on quality and outcomes as the numerator of the commonly proposed definition of value as quality / outcomes divided by cost(s).

### **Data Abstraction**

One author (LAB) reviewed articles for inclusion related to Key Questions 1 to 5 and general aspects of data on costs. Information was abstracted into a Microsoft Access database (*ACMG Value*) designed for this project. Information was entered by Key Question (or subquestions) addressed and other factors (e.g., study methods if applicable, level of review). A bibliographic database was also established in EndNote (Thomson Reuters, Carlsbad, CA) to track all literature identified and reviewed during the study. A second reviewer (GEP) was available for discussion as needed.

### **Data Analysis**

While some have debated the appropriateness of combining findings from different types of qualitative research, others consider this approach to be a strength in a review. Four methods were pre-selected for analysis in this review<sup>23-26</sup>:

- Narrative synthesis provided a general framework and description of the findings that aided in increasing the transparency of the review process.
- Thematic analysis was the identification and tabulation of important or recurrent themes.
- Content analysis added a systematic approach for identification and counting the frequency of themes, and investigating how themes related.
- Logical analysis used a logical reasoning process to develop visual representations (e.g., flow charts, diagrams) as well as detailed written descriptions.

Qualitative analysis of the findings from this review was focused on identification of themes and patterns across individual documents or qualitative studies, as well as other comparative

methods such as content analysis (e.g., counting frequency of themes), interpretive integration of findings, descriptive narrative, and logical analysis with presentation as summary or crosswalk tables and/or conceptual models (e.g., flow charts, diagrams).<sup>20,21,24</sup>

## Assessing Quality and Strength of Evidence

This step was a particular challenge for a qualitative review, as there is little consensus on quality criteria. Quality assessment methods are readily available for quantitative SERs, but the value of their use in this setting is unknown. As a first step, descriptive information was entered for included documents into the Access *ACMG Value* database, including the specific article/document type and source (e.g., peer-reviewed publication, web-posted document with URL, Institute of Medicine Report, commentary/editorial) and level of review (e.g., journal review, peer review, public comment, committee review).

Methods for assessing the quality of individual articles and documents were developed by modification of existing methods and tools.<sup>22,24,26,31-34</sup> Quality of individual qualitative research studies will be assessed using standard questions in Table B4 (Appendix B) that were developed based on comparison and modification of the existing quality frameworks.<sup>22,24,31-34</sup> Answers to questions will be documented separately or entered into the *Quality data* field of the database. Assessment of quality as *Good*, *Fair* or *Poor* will be determined based on the number and weight of study strengths and weaknesses, and documented in the *Quality data* field.

**Good** No major features that suggested risk of bias or other flaws.

**Fair** Susceptible to some bias, but flaws not sufficient to invalidate the results.

**Poor** Significant study problems that may have invalidated the results.

Quality of published or unpublished individual documents, web materials, systematic reviews and other qualitative non-research documents was assessed using a set of questions developed for this review based on concepts for document analysis<sup>26</sup>, other review in qualitative information<sup>22,24,34-37</sup>, and key dimensions for assessing qualitative information<sup>24</sup> (Table B5, Appendix B). The dimensions were credibility (*i.e.*, credibility of source, level of review, potential for specific point of view), transferability (*i.e.*, applicability of processes or standards), dependability (e.g., findings likely to be stable over time and different researchers/ methods) and confirmability (e.g., findings corroborated by others as in systematic reviews or quality consensus documents). Answers to questions were documented separately and/or entered into the *Quality data field* of the database, and overall assessment of quality as *Good*, *Fair* or *Poor* was documented in the *Quality data* field. For these materials, quality assessments were:

**Good:** Systematic review or document with internal and/or external expert or peer review, clear presentation of results based on literature or consensus (e.g., professional or advisory or committee reports).

**Fair:** Document from reliable source (e.g., white paper, government web page) with clear information, authorship and/or target audience(s), but no information on level of review; invited

commentary, editorial, opinion written by a known expert with no observed bias; otherwise good documents with an observed weakness in one or more categories.

**Poor:** Web publication from source of unknown reliability, unclear target audience and/or no information on authors or review; invited commentary, editorial, opinion from a source with unclear relevant expertise and/or suspected bias; web page with no indication of level of contribution or references; any source with insufficient information about dating/updating.

The overall level of quality of the findings for each key question (*i.e.*, strength of evidence in a quantitative review) was assessed as *Convincing*, *Adequate* or *Inadequate* using modifications of existing quality hierarchies (Table B6, Appendix B).<sup>31,35</sup> The grade for each level was determined using published approaches for determining criteria, such characteristics of findings, credibility (*e.g.*, source, level of review), objectivity (*e.g.*, level of diversity, bias), generalizability, and confirmability.<sup>31,32</sup>

## RESULTS

### Scope of Findings

The searches and review yielded a number of published articles, as well as web-based policy, consensus opinion and other documents (with exclusions per Table B4, Appendix B). Of the 98 documents abstracted into the *ACMG Value Access* database, 81 were published in peer-reviewed journals, 16 were web-based and one was a book chapter.<sup>36</sup> Among the 81 publications were 21 qualitative studies<sup>15,19,37-55</sup>, five systematic reviews<sup>56-60</sup>, five professional committee opinions<sup>6,7,14,61,62</sup>, six included editorials and commentary/perspective articles<sup>11,63-67</sup>, four review articles<sup>30,68-70</sup>, and 40 general peer-reviewed articles.<sup>1,12,13,17,52,71-105</sup> The 16 web-based materials included four Institute of Medicine Reports<sup>4,106-108</sup>, three government white papers<sup>102,109,110</sup>, two committee opinions<sup>61,62</sup>, two government resource sites<sup>8,9</sup>, and five other web-published documents (including one systematic review).<sup>5,10,111-113</sup>

Eighteen sources provided relevant information on value (KQ 2 a,b)

1,5,10,17,37,67,71,76,81,82,92,101,103,106-108,110,111, 33 on genetic diagnosis and genetic services

(KQ3)<sup>13,15,29,36,37,39-41,44,45,48-50,56,57,59,61,63,66,68,84,86,89,93,100,107,114-120</sup>, 67 on individual, family and

societal health outcomes and quality (KQ 4 a, b, c)<sup>4-10,13,14,17,19,36,38-42,44,45,48-51,54,56,59-68,70,72-79,81,83-</sup>

86,89-92,95-97,102,105-107,109,111-113,119,121,122, 31 on personal, psychosocial, societal and other outcomes

(KQ5).<sup>5,36-43,45,48,50-52,54,55,59,65,73,74,77,78,81,86,87,97,98,104,107,111,121</sup>

### Organization and Review of Information

- Relevant information (mainly narrative) was abstracted directly from the materials into database text fields in the authors' words. The objective was to avoid reviewer influence and ensure that reviewers could return to the database to check facts and reconsider the authors' intent as needed.
- Based on database fields, materials could be stratified by variables that included:
  1. year of publication or development (updates noted);
  2. peer-reviewed publication versus web-based or web-published document;
  3. type of material (select one from *general article, study, systematic review, IOM Report, government white paper; Committee opinion; web page; web published document, other*);
  4. type of review (select as many as apply from *journal review, peer review, expert review, public comment, committee review, not provided*);
  5. specific information pertaining to each Key Question; and
  6. quality criteria and rating.
- For published studies captured in the search, methods were abstracted for quality review.
- Definitions for all relevant terms were abstracted for review and possible inclusion in the glossary.
- Access reports were generated that assembled all findings related to each key question or other variable, stratified by unique ID numbers for each article/document.

- Content analysis of Access reports and abstraction forms was performed by the reviewers for each Key Question, with particular attention to:
  - identifying themes and their frequency;
  - developing clear and well-ordered narratives that describe the qualitative findings;
  - presenting and comparing identified conceptual models and data hierarchies;
  - developing summary and cross-walk tables and interpretive figures; and
  - identifying potential 'component' parts that could be assembled into a model framework for assessing the value of genetic diagnosis.

## FINDINGS FOR KEY QUESTION 1:

***Can an evidence-based and/or validated framework be identified that can be used to examine the value of making a specific genetic diagnosis, from the perspective of the patient, family, health care providers, payers, health care sector, public health and society?***

No single source was identified that provided an evidence-based and/or validated framework that:

1. addressed all components of *value* (e.g., quality/outcomes, cost);
2. addressed key perspectives (minimally patient, family, provider, society) for the components; and
3. was either specific to genetic diagnosis / genetic services or generalizable from a comparable medical specialty.

However, several sources presented important concepts and/or focus on specific content areas related to outcomes and/or value.

## FINDINGS FOR KEY QUESTION 2:

### *What can be learned from existing ‘value frameworks’ in health care?*

#### **A history and evolution of *quality* and *value* concepts and models in health care**

In 1966, Donabedian<sup>85</sup> stopped short of providing a definition of “*quality*” in the context of medical care, but proposed “*dimensions of quality*” that remain central to current models related to measurement of value in health care<sup>4,5,17,56</sup>, and quality improvement.<sup>123</sup>

- The first dimension, **outcome**, refers to change in a patient’s health status (e.g., survival, restoration of function) as a consequence of care provided. While outcomes represent a principal indicator of the quality of medical care, Donabedian noted that health outcomes reflect “..quality of care in the aggregate..” and do not provide insight into the “..nature and location of deficiencies or strengths to which the outcome might be attributed.”
- This conclusion led Donabedian to the second dimension of quality, **process**, which includes patient-provider interactions at all levels, care coordination and communication.
- The third dimension, **structure**, addresses the setting in which care takes place, including the facilities, qualified staff, and administrative / fiscal organization that support medical care.

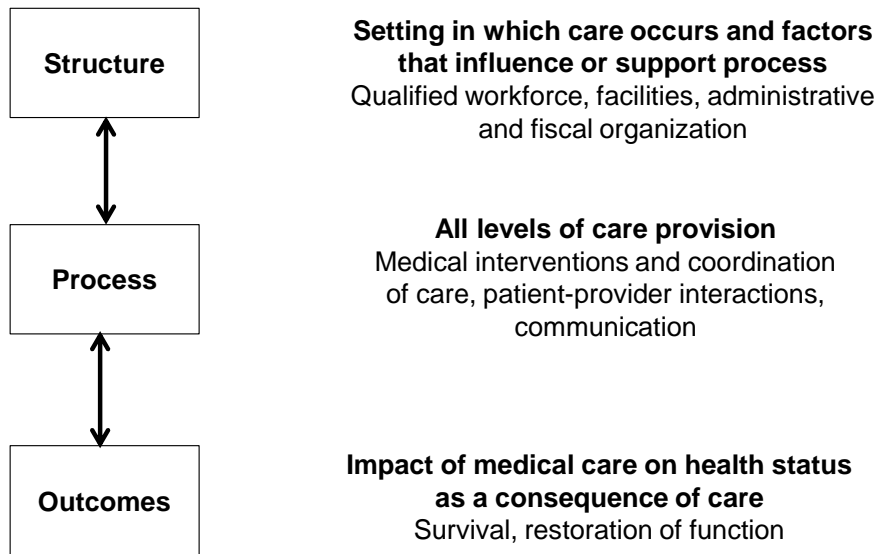
While focusing on these three dimensions of quality, Donabedian acknowledged that other dimensions (e.g., psychosocial issues, patient-physician relationship, preventive care) were often excluded from definitions of quality, and that “..many factors other than medical care may influence outcome.”<sup>85</sup> Donabedian further noted in the context of health care that “..economic efficiency deals with the relationships between inputs and outputs and asks whether a given output is produced at least cost.” The Donabedian model is illustrated in Figure 2.

In 1995, Wilson & Cleary<sup>98</sup> added a new ‘dimension’ to quality by proposing a quality and outcomes model (Figure 3) that included measures that “..describe or characterize what the patient has experienced as a result of medical care,..as useful and important supplements to traditional..measures of health status.” The goal was to try to integrate traditional clinical variables with measures of quality of life or overall well-being. *Health-related quality of life* (HRQL) was defined as “ the aspects of quality of life that relate specifically to a person’s health.” Distinct measures of HRQL include *symptoms*, *function*, *general health perceptions*, and *overall quality of life*. The Wilson & Cleary model (Figure 3) also acknowledged the environmental influences and characteristics of each individual that can affect HRQL measures.

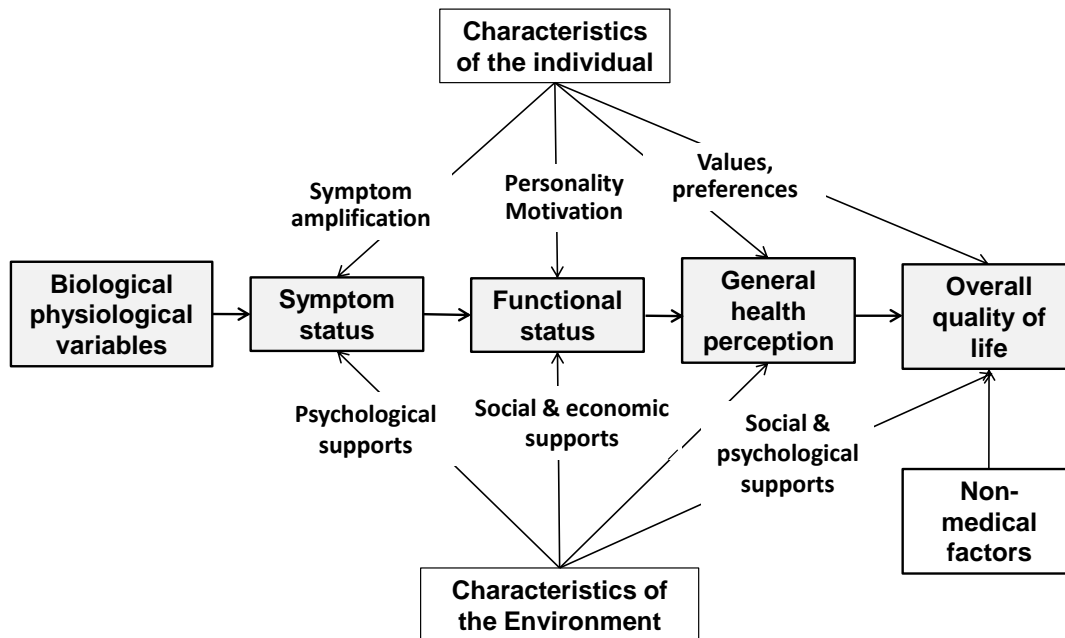
A decade later, Valderas and Alonso<sup>87</sup> returned to Wilson & Cleary as part of an effort to develop a classification system for patient-reported outcome (PRO)<sup>1</sup> measures based on a conceptual model. Their quality and outcomes model (Figure 4) integrates the World Health Organization’s International Classification of Functioning, Disability and Health (ICF)<sup>124,125</sup>

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<sup>1</sup> A patient-reported outcome (PRO) is “..the measurement of any aspect of a patient’s health status that comes directly from the patient”.<sup>81</sup> See KQ5 for a more detailed discussion.

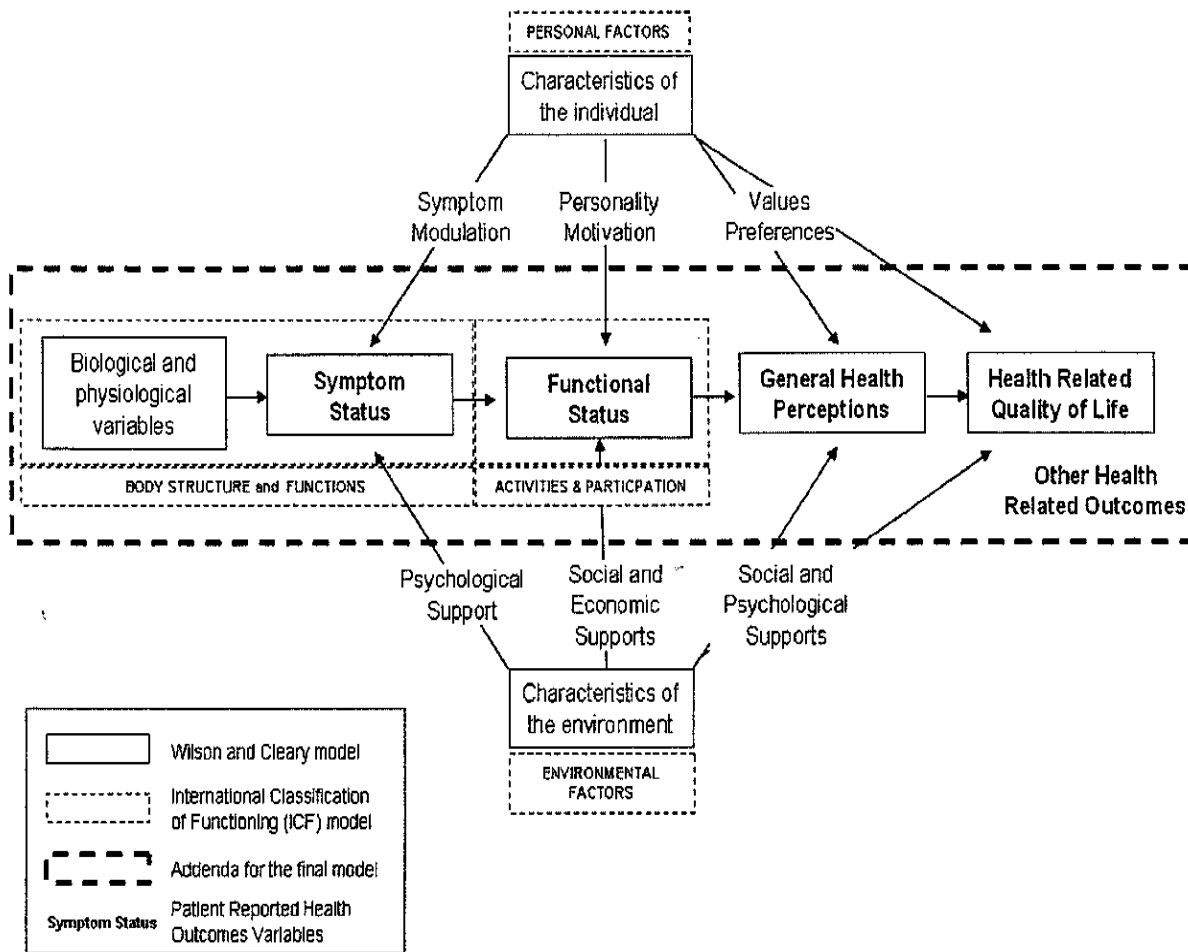


**Figure 2.** Donabedian model – Core dimensions of quality in medical care (1966)

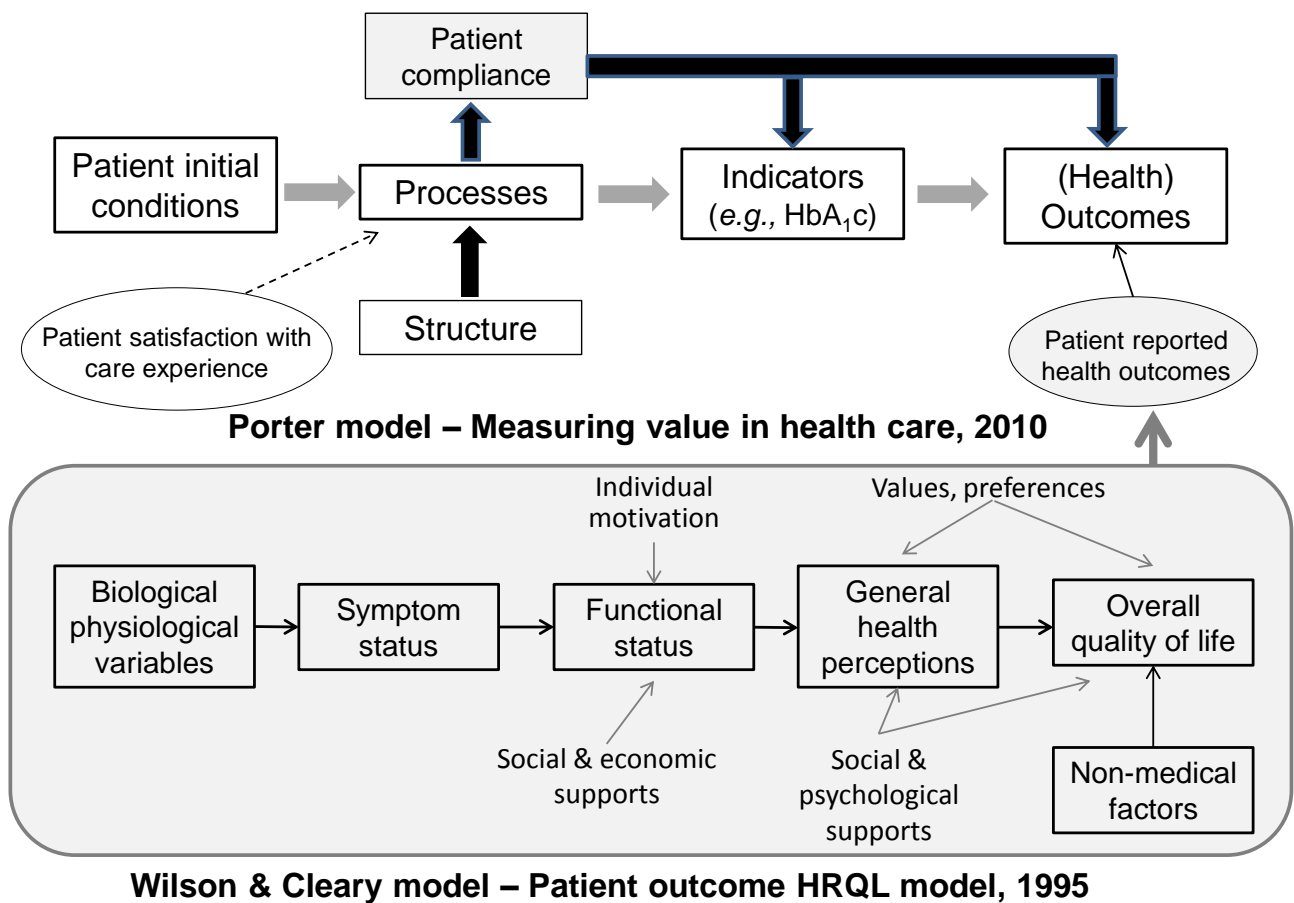


**Figure 3.** Wilson & Cleary Patient outcome and health-related quality of life (HRQL) model, 1995





**Figure 4. Valderas Outcomes Model** Integrates Wilson & Cleary model with the International Classification of Functioning, Disability and Health (ICF). The aim was to develop a classification system for Patient Reported Outcome (PRO) measures based on a new conceptual model. (Further coverage in KQs 4 and 5)



**Figure 5. Relationship of Wilson & Cleary and Porter models**

developed to “..provide a standard language and framework to describe and measure health and health-related states.” ICF is a classification of health (e.g., hearing, walking remembering) and health-related domains (e.g., education, social interactions). These domains are classified into a list of body functions and structure and lists of domains of activities and participation and environmental factors. They also further differentiated and defined the Wilson & Cleary concepts of symptom status, functional status, health perceptions and health-related quality of life. The changes to this model are not likely to have a large impact specific to this review. However, there are two points of potential interest. First, the Valderas article<sup>87</sup> highlights the continuing efforts to clarify definitions (e.g., “functional status”, “general health perceptions”) and to consider how resources (e.g., ICF) and functional concepts (e.g., patient-reported outcomes) relate to evolving conceptual models. Second, the ICF is a resource used in the US<sup>125</sup> (Figure B3, Appendix B), and may have relevance to genetic diagnoses (ICF Browser, <http://apps.who.int/classifications/icfbrowser/>).

In 2010, Porter proposed a model (Figure 5) for measuring value that integrated Donabedian and Wilson & Cleary models and introduced new concepts.<sup>10</sup> These include:

- Considering, and adjusting for, the patient’s initial condition and/or risks, as a factor that can affect “..treatment and likelihood or degree of success”.
- Acknowledging consideration of patient satisfaction with the care experience as an important process measure.
- Recognizing a component between process and outcomes, the idea of ‘quality indicators’ used as proxies for health outcomes – what might also be called ‘intermediate’ or ‘surrogate’ outcomes.
- Identifying a specific process measure, patient compliance, as having importance as a potential modifier of quality indicators and health outcomes.
- Maintaining focus on health outcomes, but acknowledging the need to consider patient-reported health outcomes (PROs) and HRQL.

Although presented as a “model for measuring value in health care”, cost was missing from the Porter 2010 model. In the accompanying articles, however, Porter emphasized the need to identify true costs of care, and defined *value* as quality (outcomes) relative to cost.<sup>5,17</sup> This concept of value was a reminder of Donabedian’s comment four decades earlier about knowing whether a given health care outcome was “produced at least cost”.<sup>85</sup>

### **A brief history of Institute of Medicine (IOM) sponsored deliberations on quality and value in health care**

IOM 2001 Consensus Report: *Crossing the Quality Chasm: A new health system for the 21<sup>st</sup> century*.<sup>4</sup>

*“Faced with such rapid changes, the nation’s health care delivery system has fallen far short in its ability to translate knowledge into practice and to apply new technology safely and appropriately.”<sup>4</sup>*

In March 2001, the IOM Committee on Quality of Health Care in America released the consensus report named above.<sup>4</sup> The objectives for this group were broad, including deciding on specific aims for health care improvement, developing rules for redesign to achieve the improvement aims, and considering how to change structures and processes to support the changes (e.g., increased application of evidence, use of information technology, aligning payment with QI, preparing the workforce).<sup>4</sup>

As part of establishing aims for improvement of the health care system, the group addressed *quality* as a “system property”. Quality was defined as “..the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.”<sup>3,4</sup> The Donabedian model was adopted for quality evaluation based on structure, process and outcomes (Table 2). The authors noted that: *“..the best process measures are those for which there is research evidence that better processes lead to better outcomes. For example, controlling blood pressure reduces mortality*

from stroke and heart disease...Similarly, the best outcome measures are those which are tied to processes of care, ...those over which the health care system has influence.”

**Table 2.** Domains of quality evaluation (Donabedian, 1966)<sup>85</sup>

<b>Structure</b>	<b>Process</b>	<b>Outcomes</b>
Access	Patient – provider interactions	Genetic-specific outcomes
Health information technology, databases	Care provision	Non-genetic-specific outcomes
Organizational services	Coordination of care	
Medical home	Quality assurance mechanisms	
Workforce education/training		

IOM 2009 Workshop Summary: *Assessing and Improving Value in Cancer Care*<sup>106</sup>

*“..patients, providers, and payors faced the growing challenge of deciding whether or not the benefits of treatments justified their expense.... **value**, which is commonly regarded in health care as the benefits of treatment weighed against its financial cost, deserves particularly careful consideration in oncology.”*<sup>106</sup>

In 2009, the IOM National Cancer Policy Forum of the Board on Health Care Services released this summary report on a workshop held in February 2009. The workshop represented a wide range of stakeholder perspectives, and deliberated on a practical working definition of value in oncology, characteristics of oncology that impact value, decisions on whether benefits of treatments justify their expense, challenges relating to health care costs, and future policy in cancer care. Some “unique challenges” related to measuring value in oncology appear to be relevant to clinical genetics as well.<sup>106</sup> For example, providers face pressure to adopt the newest technologies even when evidence is incomplete or uncertain, some genetic tests (like some cancer treatments) are among the most costly, and if a cure is not possible, efforts focus on reducing the burden of disease. Table 9-1 in the IOM report summary presents the common themes from the workshop with regard to value attributes, value metrics and key stakeholder perspectives. These themes are presented in Table 3 and Table 4 in this section.

IOM 2010 Workshop Summary: *Value in Health Care – Accounting for Cost, Quality, Safety, Outcomes and Innovation*<sup>108</sup>

*“..despite the obvious need, not a single agreed-upon measure of value or comprehensive system-wide approach to assess and improve the value of health care exists.”*<sup>108</sup>

In 2010, the IOM Roundtable on Value & Science-Driven Health Care released the above summary report of a workshop held in November 2008.<sup>108</sup> This meeting convened leaders from a wide range of stakeholder groups to discuss “..stakeholder perspectives on measuring and improving value in health care, identifying the key barriers, and outlining the opportunities for next steps.” Common themes developed in the workshop discussions included (directly quoted):

- **Urgency:** *The urgency to achieve greater value from health care is clear and compelling.*
- **Perceptions:** *Value means different things to different stakeholders, so clarity of concepts is key.*
- **Information:** *Information reliability derives from its sources, methods, transparency, interpretation, and clarity*
- **Incentives:** *Appropriate incentives direct attention and rewards to outcomes, quality, and cost.*
- **Limits:** *The ability to attain system value is likely inversely related to the level of system fragmentation.*
- **Communication:** *System-level value improvement requires more seamless communication among components.*
- **Providers:** *Provider-level value improvement efforts depend on culture and rewards focused on outcomes.*
- **Patients:** *Patient-level value improvement stems from quality, communication, information, and transparency.*
- **Manufacturers:** *Manufacturer-level regulatory and purchasing incentives can be better oriented to value added.*
- **Tools:** *Continually improving value requires better tools to assess both costs and benefits in health care.*
- **Opportunities:** *Health system reform is essential to improve value returned, but steps can be taken now.*

The report concludes that next steps will require efforts at the many levels:

- Systems – health information technology (HIT)
- Payers - coverage with evidence development, outcome-focused payment approaches), providers (e.g., identifying high-value services, care coordination incentives
- Patients - become stronger partners in communication on value, value-based payment structures
- Manufacturers - regulatory and purchase models focused on outcomes
- Research and information management – increased capacity for comparative effectiveness, analytics for value assessment

While generally forward-focused and positive, this report does caution that:

*“..defining value, let alone measuring it, is very challenging in health care, where neither benefits provided nor resources used to create the benefits are straightforward. Although there have been a considerable number of research studies using various econometric approaches to cost and benefit determination in health care, there is as yet no standard practice for measuring value or even an agreed-upon definition of value.”*

**Table 3. Proposed value components in two reports**

<b>IOM Report on Assessing &amp; Improving Value in Cancer Care, 2009<sup>106</sup></b>	<b>Porter What is value in health care?, 2010<sup>5</sup></b>
Outcome attributes: Survival, duration of life, quality of life, adverse events, time to progression and tumor response	Health outcomes Health indicators
Cost	Patient-reported health outcomes Cost
Care attributes: Access to care, quality of care, communication, social equity	Process
Patient-centered attributes: Compassion and respect, opportunity for treatment benefit, choice, hope	Structure
Innovation and future discovery	Innovations in care

**Table 4. Proposed important perspectives on value of health care**

<b><u>IOM, 2009<sup>106</sup></u></b>	<b><u>Silvey, 2009<sup>126</sup></u></b>	<b><u>Botkin, 2010<sup>119</sup></u></b>	<b><u>Committee, 2011</u></b>
Patients	Patient	Patient	Patients
Families	Family	Family	Family members
Physician or clinician	Health care providers	Physician	Health care providers
Health insurer (public & private)	Insurers (public & private)		Payers Health care sector
Society	Public health Society	Society	Public health Society
Pharmaceutical manufacturer			

## IOM 2010 Workshop Summary: *The Value of Genetic and Genomic Technologies*<sup>107</sup>

*“A need was identified for a workshop to explore the concept of value in regards to genomics and genetics and how that concept affects the views of stakeholders and the ways they make decisions about using these tests and technologies.”*<sup>107</sup>

In 2010, the IOM Roundtable on Translating Genomic-Based Research for Health of the Board on Health Sciences Policy released the above summary report of a workshop held in March 2010. The public workshop aimed to: 1) investigate the perceived value of genetic and genomic technologies clinical practice from different stakeholder perspectives; and 2) build on the concepts of analytical validity, clinical validity, and clinical utility, as well as personal utility, public utility, and economic value. Concepts were explored using three specific examples of genetic/genomic tests currently in use (e.g., Lynch syndrome testing in colorectal cancer patients, pharmacogenomic testing for warfarin dosing, genomic profiling). The discussion was not intended to focus on the value of the specific treatment or test presented, but rather to address the broader issue of how stakeholder groups view the value of using the technologies. Themes developed through discussion included<sup>107</sup>:

- There was agreement that value encompasses improvements in clinical outcome and quality of life (e.g., reduction in complications and morbidity/mortality).
- There was agreement that data on outcomes and the balance of benefits and harms are needed.
- Evidence-based medicine is key in assessing value.
- Fragmentation of the healthcare system increases the difficulty of “making the economic cost case”, because family members are often covered under different health plans.
- Barriers to data collection include “lack of motivation, lack of funding, and inadequate infrastructure”.
- Representation of genetic or genomic information in currently available electronic health records or personal health records is limited.
- Data element standardization is needed to facilitate comparison of data across health record systems.
- Ways to collect quality data more efficiently are needed.

### **Defining and Characterizing *Value* in Health Care**

Definitions of value were found mainly in recent published and grey literature, but show a reasonable level of consistency:

*“Value = health outcomes achieved per dollar spent.”* Porter, 2010<sup>17</sup>

*“..improving the net ratio of benefits obtained per dollar spent on health care.”* IOM Report, 2010<sup>108</sup>

*“In global health...defined as long-term health outcomes achieved per dollar spent.”* Kim et al., 2010<sup>92</sup>

*“..improvement in health outcomes relative to the money spent.”* Teisberg & Wallace, 2009<sup>92</sup>

“..commonly regarded in health care as the benefits of treatment weighed against its financial cost.” IOM Report, 2009<sup>106</sup>

“Care with the highest benefits relative to costs.” Baicker, 2008<sup>71</sup>

However, others are not as convinced. As noted above, one IOM report acknowledged the lack of standard approaches for measuring value.<sup>108</sup> Lee et al.<sup>101</sup> assert that “..there is not yet a shared meaning of “value” or systems in place capable of measuring it”, particularly in the area of diagnostics. Porter proposed a very specific definition for value, but acknowledged that “..value in health care remains largely unmeasured and misunderstood.”<sup>17</sup>

A European policy group<sup>110</sup> has suggested a broader definition of value that goes beyond health outcomes and HRQL to consider “..patient preferences, quality, equity, efficiency, and product acceptability among a wide range of stakeholders.” The AHRQ defines *improving value* as “..reducing unnecessary costs (waste) and increasing efficiency while maintaining or improving healthcare quality.”<sup>82</sup>

### Components of Value

Two sources provided the most in-depth consideration of the components of value. The 2009 IOM Report *Assessing and Improving Value in Cancer Care*<sup>82,106</sup> proposed five ‘attributes’ of value (Table 3). The Porter model for measurement of value<sup>5,10,17</sup> has a clear focus on health outcomes and cost, but also includes the domains of health indicators (*i.e.*, intermediate, surrogate or proxy outcomes), process measures (*e.g.*, patient compliance), patient-reported health outcomes (*e.g.*, function, HRQL), and structure measures. The two sources show some areas of consistency (Table 3). Porter’s use of ‘process’ may be somewhat broader, but appears to include the IOM ‘care attributes’. ‘Structure’ measures were not included among the IOM value attributes. The inclusion of ‘innovation’ in both was interesting, and seems to imply a positive view of value measurement as supporting opportunity for innovation and future discovery.

Porter<sup>17</sup> stated that the “..proper unit for measuring value should encompass all services or activities that jointly determine success in meeting a set of patient needs”, and emphasized that value in health care is not measured by the volume of services delivered, but rather by the outcomes achieved. Proper measurement of value should include the multiple interventions (potentially by multiple health care providers) over the full cycle of care. For primary and preventive care, value must be measured for defined patient groups with similar clinical characteristics and needs (*e.g.*, patients with a specific chronic disease, healthy adults, patients with multiple chronic conditions).<sup>17</sup> Value of health care is also not measured by processes of care; such measurements may be useful but cannot replace measuring outcomes and costs.<sup>17,75</sup> However, a subset of process measures may have significant impact on outcomes. For example, there is good evidence that patient compliance with treatments, rehabilitation, and preventive measures can have an effect on outcomes. However, systematic measurement of patient compliance appears to be lacking in most health care systems.<sup>5</sup>



One source stated that the *value of laboratory tests* could be assessed by examining safety, efficacy, feasibility, effectiveness, appropriateness, and cost...as well as other clinical, social, economic and ethical implications related to their use.<sup>111</sup> Another proposed only three dimensions of *diagnostics value*: medical value (e.g., ability to inform clinical treatment); planning value (e.g., ability to inform patients about long-term health, reproductive options); and psychic value (e.g., ability to affect patient's sense of well-being if treatment is unavailable or ineffective).<sup>101</sup>

The United Kingdom's National Institute for Health and Clinical Excellence (NICE) concluded that the *value of a treatment* is based on scientific value judgments, including clinical and economic evaluation, social value judgments, and considerations of efficiency and effectiveness".<sup>109</sup>

### Value Metrics

The IOM Report *Assessing and Improving Value in Cancer Care*<sup>106</sup> proposed:

- Economic metrics – Quality adjusted life years (QALYs) or cost per QALY
- Care metrics – Quality of clinician-patient communication, coordination of care
- Equity metrics – Variation or disparities in care, workforce or service shortages
- Innovation metrics – Willingness to pay for treatment research, generics, new products

The Care metrics and one Equity metric (variation/disparities in care) could also be categorized as process measures; workforce or service shortages could relate to structure measures. It is not clear whether these metrics are meant to be considered individually or, alternatively, or how results might be aggregated to provide an overall metric for the value of a health care service or intervention.

In summary for KQ2, the definition of *quality* proposed by Lohr in 1990<sup>2,3,108</sup> as “..the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge”, was adopted by the IOM in 2001<sup>4</sup> and later by the American College of Medical Quality. The literature showed some consistency in definitions of *value* in health care over the last four years, and specific information on components of value was limited but consistent (Table 3). However, findings were insufficient to support a consensus vision of value in health care generally or in genetic diagnoses, or how to measure it.

There has been some consistency in the evolution and themes in the identified models related to quality / outcomes in health care<sup>5,59,85,87,98,126</sup>, although the impact of these models on thinking in clinical genetics or health care in general is unknown.<sup>17,85,87,98</sup> The Donabedian model<sup>85</sup> most commonly appears in articles about quality and quality improvement, probably related to its simplicity and general applicability.

Three reports<sup>80,106,126</sup> and representation at IOM workshops<sup>4,106-108</sup> were consistent with the Committee's view of key stakeholder group perspectives. However, It is difficult to draw overarching conclusions from the IOM reports<sup>4,96-98</sup> of meetings on value in health care, as each

had a slightly different focus and meeting format. In addition, each had different levels of representation from key stakeholder groups, so were too limited to adequately differentiate between a group versus a personal perspective. For this review, the first meeting<sup>4</sup> was most relevant for the specific output on components of quality, the second on components and metrics of value<sup>106</sup> and the third on barriers and opportunities for achieving value in health care<sup>108</sup>. The fourth specifically addressed genetic and genomic technology, but was less focused in terms of output (e.g., conclusions and possible next steps); some of the collated themes were developed from the narrative by the reviewer.<sup>107</sup> Overall these findings provide historical perspective and, perhaps, a foundation on which to build next steps for addressing quality and value in clinical genetics.

### **Quality of Findings**

Among the 17 individual general articles/documents addressing KQ2, six were graded *Good*; 10 *Fair* and one *Poor*; the one primary study was graded *Fair*.

The overall knowledge generated was classified as *Adequate* for:

- quality and value concepts that are likely to be generalizable;
- value terminology and components;
- quality / outcomes models that raised issues and suggested potential approaches for future work; and
- a reasonable level of diversity in perspectives.

However, most existing value measurements appear to have been based on quality adjusted life years (QALYs), the metric of economic analyses. The second stage of review on costs and economics discussed in Methods is needed to assess the applicability of the QALY metric across different genetic diagnoses and their health outcomes, as well as the appropriateness and validity of the health and other outcomes selected to assess value and the degree to which outcomes data was collected or modeled. Another key point for future review is the extent to which value measurement approaches have been piloted in real world clinical settings, and what is known about potential strengths and weaknesses of these approaches.

### FINDINGS FOR KEY QUESTION 3:

#### ***How should genetic diagnosis be defined? What are the components of genetic (or other) diagnoses (e.g., clinical criteria, testing, family history, intervention / therapy)?***

As part of the planning for this review, the TEP and reviewers developed a list of the principal components of a 'classical' genetic diagnosis as:

- Clinical examination
- Medical history
- Family history
- Genetic counseling
- Follow-up / confirmatory testing based on results of screening tests
- Procedures / non-laboratory testing
- Genetic laboratory testing
- Records/data review and consultations
- Communication of information to patients<sup>57,59</sup>
  - Medical facts and hereditary nature of the diagnosed disorder or condition
  - Available clinical or other intervention(s) and options
  - Effectiveness of intervention(s) and what is known about the balance of benefits and harms
- Costs

The first seven components are standard clinical services that could be involved in a genetic diagnosis. The eighth component, communication of information, is, of course, integral to all, but is acknowledged to be sufficiently important in clinical genetics to be considered a unique component. Financial costs are not commonly included in such a list, but awareness of the need to consider and document "true" costs of a genetic diagnosis is crucial if the goal is to measure the value of individual clinical genetic diagnoses. Another component of clinical genetics care beyond the genetic diagnosis, the ongoing / long-term management of genetic disease and of transitions in care (e.g., pediatric to adult), was also suggested to be an element of value that may warrant inclusion (personal communication, expert reviewer).

The Committee posed a similar question about components of a genetic diagnosis to members of the ACMG Laboratory Quality Assurance Biochemical Genetics (n=3), Cytogenetics (n=5) and Molecular Genetics (n=4) Subcommittees.<sup>127</sup> A single person documented and compiled responses to the question: *What are the components of a genetic diagnosis (i.e., role of clinical criteria and genetic testing)?*:

- Identification of the disorder and potential intervention(s)
- Integration of laboratory and clinical data to determine the exact etiology of the disorder, consider potential therapy and provide accurate risk assessment for other family members
- Process begins with suspicion of a genetic disease or risk of a genetic condition; other components may include:

- Family history
- Past medical history
- Evaluation by a Clinical Geneticist and establishment of a differential diagnosis
- Possible genetic counseling and/or informed consent
- Appropriate testing and result interpretation
- Possible referral to other specialists
- Possible literature review

### **‘Classic genetic diagnosis’ as part of clinical genetics services**

In 2001, Kaye et al.<sup>89</sup> described *clinical genetics* as providing comprehensive services to “..patients, families and populations who have, or are suspected of having, hereditary, inherited or congenital disorders.”<sup>89</sup> Today, the accredited professionals providing these services are Clinical/ Medical Geneticists, Molecular Genetic Pathologists, Genetic Counselors and Genetic Nurse Associates. Clinical/Medical Geneticists may have expertise and/or board certification in one or more areas that include:

Dysmorphology	Cancer genetics
Biochemical/metabolic genetics	Pharmacogenetics
Teratology	Public health genetics
Cytogenetics	Prenatal/reproductive genetics
Molecular genetics	Neurogenetics
	Cardiovascular genetics

In addition to direct patient care, Clinical Geneticists may oversee newborn screening programs and laboratories that establish or confirm diagnoses of genetic disorders. With improved knowledge and technological advances, genetic laboratory services have expanded, offering a rapidly increasing number of genetic (particularly molecular) tests for more conditions. In the future, increasing knowledge of molecular biological pathways offers the potential for improved care using new options for managing and treating genetic conditions.<sup>48,59</sup> Clinical genetics is noted to be a component of all medical specialties, and is applicable to patients, families and populations at all stages of the life cycle.<sup>89</sup>

Clinical genetic diagnosis is supported by laboratory practice, genetic counseling and other specialist services. Genetic diagnoses can be made through a variety of approaches other than cytogenetic and molecular tests, including physical examination (e.g., skin lesions, dysmorphology), family history, medical history, routine hematology, chemistry or pathology studies, and imaging studies.<sup>93</sup> Then, and today, diagnosis of genetic disorders requires exercise of clinical skills and experience. Cognitive services (e.g., diagnosis, management, counseling) tend to be undervalued in all areas of medicine when compared to laboratory and procedural services.<sup>114</sup> This is particularly true in the provision of clinical genetics services, where the information gathered during one clinical encounter or episode of care is rarely a true indication of the activity generated and resources expended by the clinical geneticist and/or genetic counselor in support of that referral.<sup>61,114,115</sup> Reasons can include the need for<sup>114,116</sup>:

- generation of a detailed three generation pedigree;

- collection and review of medical records of affected relatives and/or examination of relatives;
- literature review for rare disorders;
- selection and interpretation of laboratory tests;
- in-depth genetic counseling to discuss implications for the patient and family members;
- detailed documentation of the visit that informs referring physicians about rare disorders; and
- detailed summary letters for the patient and family.

Clinical genetics has evolved significantly since emerging as a medical specialty in the 1970's. At that time, persons referred to genetics clinics were mainly offered pedigree analysis, clinical diagnosis of malformation syndromes or rare familial conditions and counseling services to support informed decision making.<sup>59,61</sup> Clinical genetics had "...very little to offer in the way of treatment"<sup>107</sup>, making provision of information a prime objective of most consultations. Today, however, clinical genetics encompasses a complex set of interventions and services, provided according to the needs of the patient or family.<sup>45,48</sup> While cures may not be available for many rare genetic diseases, the number of available interventions is increasing.

These include timely identification and treatment of disease manifestations, in which genetics professionals are involved as providers of direct management and/or referral for other specialist care. Examples include:

- aortic surveillance in patients with Marfan syndrome to avoid aortic dissection<sup>128</sup>;
- when imaging (e.g., head MRI) rather than vision or hearing screening is warranted in patients with neurofibromatosis to identify optic glioma or acoustic neuroma<sup>35,129</sup>;
- the application of the "diagnostic test" for Duchenne or Becker muscular dystrophy to identify carriers of these disorders who should be made aware of the risk of developing cardiomyopathy and referred for evaluation by a cardiac specialist<sup>130</sup>;
- the medical and surgical options to maintain mobility and improve quality of life in patients with skeletal dysplasias<sup>131</sup>;
- early and/or enhanced cancer surveillance in individuals with hereditary cancer syndromes;
- gene expression profile tests for women with specific breast cancer characteristics that provide information about prognosis (e.g., recurrence risk) and/or treatment selection; and
- dietary changes and/or medical foods in patients with metabolic disorders (e.g., PKU).

Individuals having, or at risk of transmitting to their children, a disease or condition for which there is no effective intervention receive detailed counseling about the disease, information about available medical and personal support services and reproductive options. Payne et al.<sup>59</sup> note that when "...there is a...complex set of outcomes that often offer little in the way of traditional health gains...social and family issues may be as significant, and perhaps in some cases more significant, than health-related outcomes." Even when effective preventive

measures or treatment are available, the harms and benefits associated with the interventions can remain the primary outcomes of interest to patients.<sup>45</sup>

## **Genetic Counseling**

*“Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following:*

*Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.*

*Education about inheritance, testing, management, prevention, resources and research.*

*Counseling to promote informed choices and adaptation to the risk or condition.”*

National Society of Genetic Counselors Task Force Report, 2006<sup>132</sup>

Others have described genetic counseling as a “dynamic psychoeducational” communication process, through which patients (or their family members) receive information about the disorder or condition, its clinical course, available intervention(s) (e.g., treatment, management/care, medical and social support), prognosis and reproductive options.<sup>61,84,89</sup> Crucial roles of genetic counselors have been characterized as presenting information in a way that “..minimizes psychological distress and increases personal control”, as well as simplifying and personalizing “..technical and probabilistic genetic information to promote self-determination and enhance the ability to adapt over time.”<sup>61,84</sup>

As with other interventions in clinical genetics, goals and expectations of genetic counseling can be unclear to both providers and clients/patients, and there has been limited agreement on the best outcome measures.<sup>37,133</sup> It has been proposed that the ability of patients to understand, find meaning in and adapt to genetic information is related to their background, needs and expectations. Consequently, genetic counselors try to tailor genetic counseling based on these patient characteristics, and patients tend to evaluate their experience “based on how well genetic professionals meet their needs and expectations”.<sup>37,49,84</sup>

Genetic counseling outcomes would include structure (professional qualifications and certification), process and outcome measures. (see also KQ5)

## **Communication of risk to family members**

A distinctive characteristic of clinical genetics is the need to consider the implications of a genetic diagnosis not only for the person being evaluated in the genetics clinic, but also the potential risk for that person’s family members.<sup>57</sup> As has been noted, communication of risk is a central activity in clinical genetics, with genetic health professionals sometimes facing the additional responsibility of encouraging a patient to consider dissemination of relevant information to at-risk family members. The extent to which the clinical geneticist should be

responsible for ensuring that family members are informed about their risk has long been debated. Based on a 2007 systematic review on communication of genetic information within families, Gaff et al.<sup>57</sup> reported:

*"Family communication about genetic risk is described as a deliberative process, in which: sense is made of personal risk; the vulnerability and receptivity of the family member is assessed; decisions are made about what will be conveyed; and the right time to disclose is selected. The communication strategy adopted ...varies within families as well as between families. Inherent in these processes are conflicting senses of responsibility: to provide potentially valuable information and to prevent harm that may arise from this knowledge.*

*In contrast to infectious diseases, communication of genetic risk to those considered at risk is 'ethically dubious' in nature, with a lack of clarity about what individuals should reasonably be expected to do, and how professionals should respond when they are aware that communication within a family has failed or is blocked. This will depend in part on the nature of the information available (risk information only or genetic test results) and implications of the condition....In general, there seems to be an uneasy consensus that genetic services should rely predominantly on the consultant to convey information, except in exceptional circumstances."*

A summary paragraph was provided by the Committee Chair, Dr. Marc Williams, as background for this review is included here as a clear statement of the challenge facing clinical genetics in addressing value:

*"Genetics as a profession has struggled with quantifying the value it brings to health care. This has resulted in barriers to reimbursement for tests and services as well as challenges for support of geneticists and genetic counselors within healthcare delivery systems. There are numerous challenges to defining value including the rarity of most disorders we treat, the general lack of therapeutic interventions and difficulties tracking downstream medical and financial impact of genetic consultations. As a profession, we have not adequately defined outcomes of interest. While we suggest that a genetic diagnosis can alter care, eliminate the need for a diagnostic odyssey and impact the health of other family members, with a few exceptions, we have not generated sufficient evidence of benefit."*

In summary for KQ3, the literature tends to focus more broadly on the components of *clinical genetic services*, but is generally consistent with the descriptions of a *genetic diagnosis* and its component parts. Key themes are:

- the comprehensive scope of clinical, educational and supportive services offered as part of a genetic diagnosis;
- the importance and added value of effective communication of information and risk to patients and family members by genetics professionals; and
- the need to make the case for the value of genetic diagnosis and other clinical genetic services to payers and policy makers.

## Quality of Findings

Among the 19 individual general articles/documents addressing KQ3, 10 were graded *Good*; eight *Fair* and one *Poor*. Among the 10 studies; three were graded *Good* and seven *Fair*.

The overall knowledge generated was classified as *Adequate*, but in this case represented more descriptive and practical information that perhaps showed less diversity, but provided more focus on a specific perspective or topic (e.g., clinical genetics), and identified issues for consideration related to current practice. A key limitation was the small amount of consensus information from some important perspectives (i.e., more than a single payer representative providing opinions at a meeting).



## FINDINGS FOR KEY QUESTION 4:

***How does establishing a genetic (or other) diagnosis in an individual impact the balance of benefits and harms related to short- and long-term health outcomes?***

- a. What are specific health outcomes of interest to the individual patient? How does establishing a genetic (or other) diagnosis contribute to improved short- and long-term health outcomes of patients?***
- b. What are specific health outcomes of interest to patient's family members? How does establishing a genetic (or other) diagnosis contribute to improved short- and long-term health outcomes of family members?***
- c. What are specific health outcomes of interest to health care delivery systems and/or public health programs? How does establishing a genetic (or other) diagnosis contribute to measurable improvement in short- and long-term health outcomes from these perspectives?***

*"(Health care) increases value by improving outcomes for patients. Without measures, providers live in the health care district of Garrison Keillor's Lake Wobegon. They each assume that the health outcomes of their patients are above average. Those with a more realistic assessment of their patient's health outcomes can rationalize the results by assuming that their patients are more complex." Teisberg & Wallace, 2009<sup>92</sup>*

*"Efforts to measure outcomes must begin with imperfect measures, but fortunately the fastest way to improve outcome measures is to start using them."<sup>92</sup>*

## **Approaches for Collecting Data on Health Outcomes**

Most data on health outcomes were collected through clinical and health services research (e.g., randomized controlled clinical trials, other clinical trial designs, observational studies, qualitative studies). Research also includes systematic review of published primary quantitative and qualitative research studies and economic evaluations. Other "real world" processes include public health initiatives (e.g., Newborn Screening Genetics Collaboratives), disease registries, and health surveys. Review of administrative data, electronic medical records and medical chart reviews have been undertaken as part of QI or other internal or collaborative health provider initiatives.<sup>59,134</sup>

Resources and time allocated for this review did not allow for a comprehensive search of the research literature on outcomes for a range of genetic diseases. Rather, the intent was to identify existing frameworks intended to assist in the process of determining what types of outcome measures (*i.e.*, structure, process, health outcome, other outcome) should or might be considered within the general category of "genetic diagnoses", and how more disease-specific measures might be derived. It is not surprising that the literature selected did not provide many

disease-specific findings related to outcomes. However, to provide this important perspective, three disease-specific examples are provided later in this section.

## Health Outcomes

Based on the findings from the initial search for outcome frameworks, very little objective evidence was identified to quantify the impact of genetic diagnoses on short- and long-term health outcomes, with the possible exception of newborn screening. Genetics is not unique, as evidence in other areas of health care is also limited.<sup>5,10,13,17,36,45,56,59,60,84,107</sup> It was noted in 2010 that in health care, “..systematic, rigorous outcome measurement remains rare.”<sup>17</sup> However, the literature does provide a range of materials on relevant deliberations in the US, applicable concept and model development, and some existing measurement processes. At this time, such processes are mainly focused on structure and process outcomes, and do not directly assess health outcomes to any degree. However, the lessons learned are likely to be applicable.

A health outcome can be broadly defined as “ a change in a patient’s health status (e.g., survival, restoration of function) as a consequence of health care provided.”<sup>85</sup> Porter contends that *quality in health care* should refer specifically to patient outcomes, with quality relative to cost then determining *value*.<sup>5,10</sup> As noted previously *quality* has various meanings<sup>2-4,7,19,85</sup> and is sometimes more broadly associated with basic process/service measures or safety.<sup>19,85,118</sup>

For the purposes of this review, the concept of *quality = patient health outcomes* has been adopted for this review, but with two caveats. First, it is not yet clear how broad the definition of patient health outcomes will need to be for clinical genetics. Second, the related concepts of “clinical utility” and “personal utility” must be considered, as well as the evolution of these terms as part of the emergence of genetic and genomic testing.

### Clinical Utility and Health Outcomes

The 1997 NIH-DOE Task Force on Genetic Testing report proposed three criteria for the evaluation of genetic tests: analytic validity, clinical validity and *clinical utility*.<sup>135</sup> They referred to clinical utility as representing the “..*data needed to demonstrate the benefits and risks that accrue from both positive and negative (test) results*”. In 2000, the Secretary’s Advisory Committee on Genetic Testing added to the concept:

*“Clinical utility takes into account the impact and usefulness of the test results to the individual, the family and society. The benefits and risks to be considered include the psychological, social and economic consequences of testing as well as the implications for health outcomes.”*<sup>136</sup>

The ACCE framework<sup>137</sup> focused on health outcomes as the primary evidence for clinical utility, but also considered contextual and implementation issues. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group<sup>138</sup> defined clinical utility of a genetic test as:

“..the evidence of improved measurable clinical outcomes, and its usefulness and added value to patient management decision-making compared with current management without genetic testing.”

However, others have continued to focus on the narrower view that: “Clinical utility refers to the likelihood that the test will lead to improved health outcomes.”<sup>139</sup>

In 2006, Grosse and Khoury<sup>64</sup> attempted to put the varying definitions of clinical utility into perspective in the context of genetic testing. They proposed that, in the narrowest view, clinical utility translates to test results that lead to an intervention/treatment that impacts (e.g., prevents, improves) health outcomes such as mortality, morbidity or disability. More broadly, clinical utility might refer to shorter-term outcomes, such as “informing decision-making”. The authors further note that, “in its broadest sense, clinical utility can refer to any outcomes considered important to individuals and families (e.g., reproductive decisions and psychosocial support).”<sup>64</sup> Such outcomes are often referred to as *personal utility*.<sup>65,77,107</sup>

The term clinical utility has been most commonly used in genetics and genomics as part of test evaluation. More recently, it has been adopted more broadly in clinical laboratory practice. However, its overarching definition as representing the balance of benefits and harms associated with the use of a test and subsequent treatment is completely consistent with the approach of the US Preventive Services Task Force in assessing clinical interventions of all kinds (i.e., evaluating the magnitude of net health benefit as benefits minus harms). As discussed above and illustrated in Table 5, the term clinical utility appears to include a range of

**Table 5.** Linking the continuum of clinical utility definitions from the genomics literature to other terminology

Clinical utility <sup>64</sup> →	Measures	← Outcomes of health care
“Narrow definition”	Morbidity, mortality, disability, function  Patient-reported outcomes (e.g., functional status)  HRQL	Long-term health outcomes  Patient-reported outcomes
“Broader definition”	Patient/physician decision-making Accuracy of diagnosis Avoidance of diagnostic odyssey Adverse effects of treatment	Shorter-term outcomes
“Broadest definition”	Psychosocial impact Perception of risk Overall QoL Knowledge/control Reproductive decisions	Other patient outcomes

outcomes. For that reason, the term “outcome” will continue to be used in this review, with acknowledgement of the clear links between health outcome and HRQL measurement and clinical utility and between a range of non-health-related outcomes of importance to patients and “personal utility”.

“Health outcomes” from the literature include mortality, morbidity, functional capacity, inaccurate diagnosis, pain/pain relief, adverse events, degree and sustainability of recovery and quality of life.<sup>4,13,17,48,67,75,81,85,106,111</sup> For longer-term outcomes (e.g., sustainable recovery, mortality) with ongoing interventions, accurate measurement requires tracking patient outcomes and costs longitudinally.<sup>17</sup> Outcomes, the numerator of Porter’s value equation, are inherently condition-specific and multidimensional, and any single outcome measure cannot capture the results of health care. Consequently, the relative merit of selecting competing outcomes for measurement needs to be considered with regard to complexity, cost, timing and other variables.<sup>17</sup> The fact that outcomes represent the results of patients’ health over time distinguishes them from single health event-related *health care processes* and from *biologic health indicators* (e.g., HbA<sub>1c</sub>) that are indirect predictors of results.

Health indicators like HbA<sub>1c</sub> are known by many synonyms: *intermediate endpoints*, *intermediate outcomes*, *surrogate markers* and *proxy measures*. For diseases like diabetes mellitus and heart disease, the goal is to measure outcomes of morbidity and mortality, but the disease process is slow and follow-up could last for decades. Health indicators may be used when it is not possible to measure what you want or need, but you need to measure something close enough to reflect similarity.<sup>123</sup> Examples for heart disease might include the proportions of:

- hypertensive patients with blood pressure at or below goal;
- diabetic patients with LDL ≤ 100; or
- myocardial infarction patients on beta blockers and/or aspirin.

There are instances in which intermediate end-points or surrogate markers are offered as evidence of clinical effectiveness, “..but the likely (low) predictive value of such measures may require clinical judgment” in their use”.<sup>109</sup> Of even more concern are intermediate end-points that appear to be sound on theoretical grounds, but have not been validated in practice.<sup>109</sup>

The lines between health care outcomes and health care processes can be unclear. For example, patient satisfaction with care can be considered a process measure, patient satisfaction with health an outcome measure.<sup>5</sup> Garrison et al.<sup>78</sup> suggested that it can be important to differentiate certain “clinical outcomes” such as patient-reported outcomes and HRQL from more narrowly defined “health outcomes”, but it is not clear where such lines could or should be drawn. Process and structure measures will be briefly described in the next section.

Many measurements have focused on survival as a health outcome that is relatively easy to measure, but there appear to be many factors of equal or greater significance to patients than

survival. With regard to functional outcomes, physicians' assessment of patients' level of functioning may differ significantly from the patient's perception.<sup>13</sup> As a consequence, more attention is being paid to patient-reported outcomes (PROs), through PRO surveys that assess process measures related to reports and ratings of health care, as well as health outcomes such as symptoms and other aspects of well-being, functioning (e.g., ability to fill needs and response to restrictions), general health perceptions, and quality of life.<sup>43,59,78,98,111</sup> (see KQ5)

In 1966, Donabedian classified outcomes as a "dimension" of value, and observed that the validity of outcome measures such as recovery, restoration and survival is not questioned in most situations and in most cultures.<sup>85</sup> He noted, however, that before using outcome measures, there should be consideration of whether:

- outcome is the most relevant measure;
- factors other than medical care may have influenced the outcome; and
- the difficulties of measuring outcomes other than mortality can be effectively overcome.

Even having overcome barriers to outcomes measurement, there remains the question of what will be done with the information. Gray et al. noted that:

*"The aim is not just to measure, but rather to use those measurements as a foundation for making changes that are improvements. We should not be content with having indicators; we should also ensure that resources and capacity are in place to learn from the measurements and to change and improve services."*<sup>63</sup>

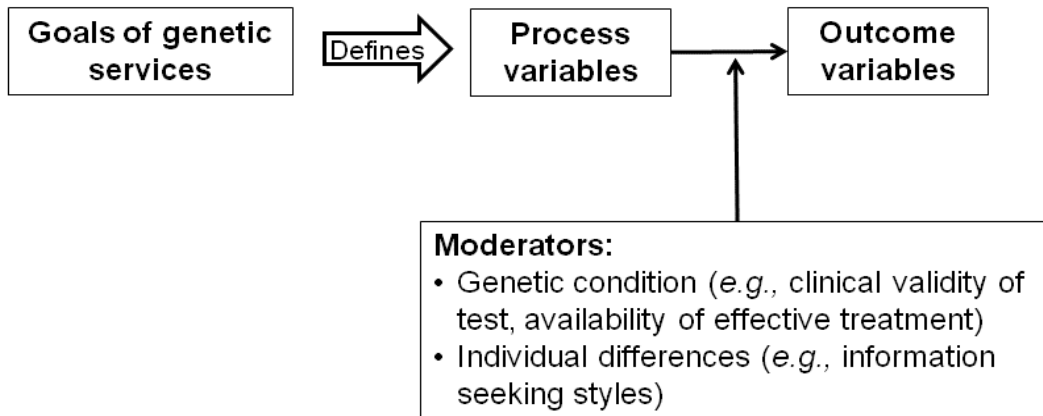
## **Outcome hierarchies identified**

### Framework for Evaluating Genetic Services<sup>84</sup>

Responding to the need to define what constituted "success" for clinical genetics services and genetic counseling, Wang et al.<sup>84</sup> developed a framework for evaluating genetic services (Figure 6). They began by "reviewing the goals and desired outcomes of genetic services", focusing on predictive testing for later onset diseases. They note that a limiting factor in developing outcome criteria is that terms and concepts are often not well-defined (e.g., informed decision-making, risk comprehension, psychological distress, patient satisfaction). To the point at which this article was written, most studies had assessed psychological reactions to testing, and were only beginning to look at decisions following testing (e.g., treatment or reproductive decisions) and subsequent health behaviors. Six areas were identified in which the authors suggested that outcome measures should be developed, based on relevance to predictive testing and impact on research priorities:

- perceived personal control – cognitive, behavioral and decision control
- meeting patient expectations – satisfaction, uncertainty reduction, quality of life
- genetic counseling processes
- informed decision-making and decision processes – decisional conflict, decision satisfaction, decision persistence vs change in decision, adherence to therapy
- system-based outcomes

**Figure 6.** Framework for evaluating genetic services (Wang et al., 2004)<sup>84</sup>



- 
- health status – emphasized long-term health outcomes and improvements in public health

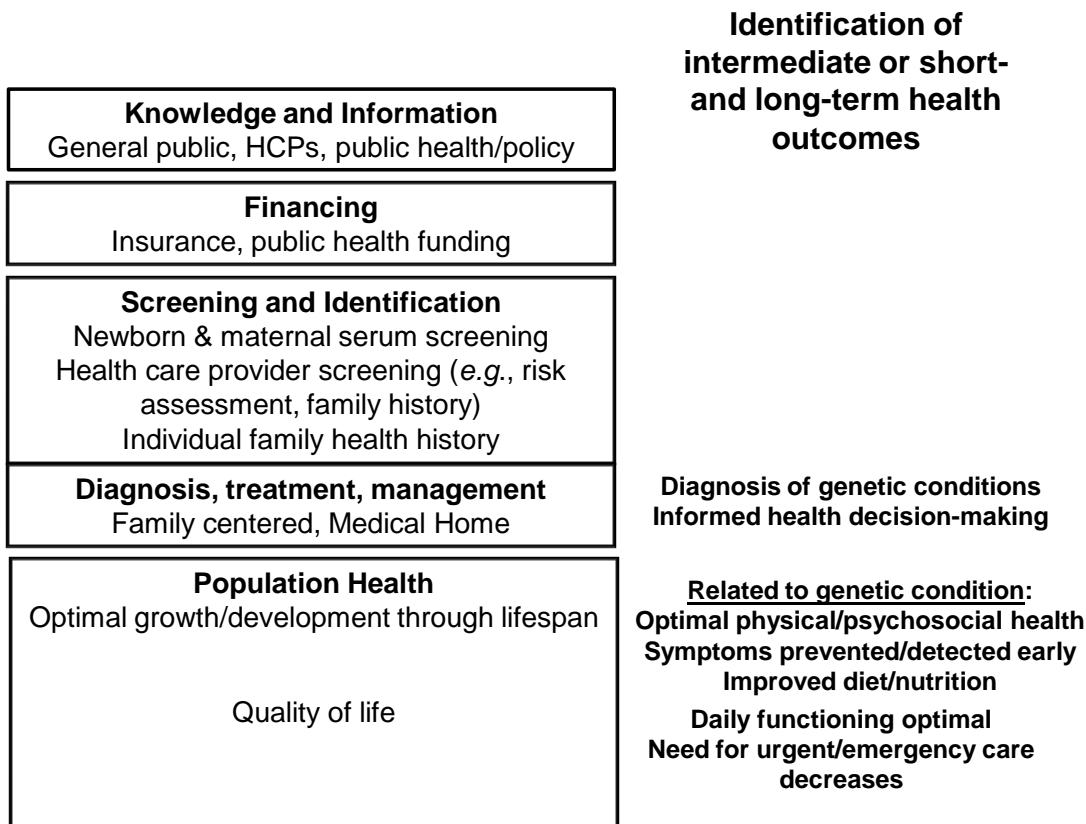
Other issues recommended for consideration were complexities associated with genetic conditions, methodological limitations of studies, and unintended effects of genetic technologies.

#### Genetics-Specific Validated Outcome Measures<sup>59</sup>

In 2008, Payne et al.<sup>59</sup> reported validated outcome measures for clinical genetic services identified from a systematic literature review. “Subjective outcomes measures” were considered to be validated only if some form of “psychometric assessment” was reported. From 61 articles, they identified 67 validated outcome measures. Among these 67, 30 were genetics-related, and 11 of 30 described three “objective outcome measures”. Four measured testing accuracy (assumed to be analytic validity) and four measured diagnostic accuracy (clinical validity); three related to the outcome of termination of pregnancy. The other 19 articles described one process measure (satisfaction with care) and a collection of general quality of life and other non-health-related patient-reported measures (e.g., knowledge, perception of risk, worry). The complete list of “genetics-specific validated outcome measures” can be found in Table B7 (Appendix B).

#### Outcomes Menu for Public Health and Clinical Genetics Services<sup>126</sup> (Figure 7)

In their 2009 report, Silvey et al.<sup>126</sup> cited the reason for this project as the growing need for clinicians and public health agencies to justify programs and services through documentation of outcomes for third party payers, lawmakers and funding agencies. In 2006-2007, a work group of genetics and public health professionals, clinicians and family representatives began a process of “identifying health outcomes of genetic services that could be used by multiple stakeholders to measure effectiveness of both public health and clinical genetics services.”<sup>126</sup>



**Figure 7. Public Health and Genetics Services Outcomes Menu** (Silvey et al., 2009)<sup>126</sup>

They determined that outcomes chosen should be:

- not condition-specific;
- practical to measure, preferably using existing data; and
- useful to stakeholders.

Based on the results of a peer-reviewed literature search, the group compiled a list of outcome concepts for discussion. During the subsequent deliberation process, a decision was made to revise the original plan and compile a more comprehensive list of outcomes. The complete Genetics Services Outcomes Menu can be found in Table B8 (Appendix B). Several approaches for organizing the information were considered, including:

- 1) concept themes based on content of the outcomes information;
- 2) a logic model framework of short-, medium- and long-range outcomes; and
- 3) categorization of outcomes as:
  - Knowledge and Information;
  - Financing;
  - Screening and Identification;

- Diagnosis, Treatment and Management; and
- Population Health.

The third option was selected. Each of these categories was then further stratified. For example, Knowledge and Information was stratified by audience (General public, Health care providers, Others), and Diagnosis, Treatment and Management as “Family centered” or “Medical home”. The detailed text in Table B7 was searched for references to health outcomes. Six health outcomes were identified (Figure 7), though the classification into intermediate, short-term and long-term outcomes is debatable in some cases. (See also KQ5)

#### Model-Based Classification System for Patient-Reported Outcomes (PROs)<sup>87</sup>

Health-related quality of life (HRQL) is perhaps the most important measure to arise from the significant expansion in health outcomes measures. Definitions of HRQL and related concepts such as *health status* and *perceived health* have varied. The Centers for Disease Control and Prevention (<http://www.cdc.gov/hrqol/>) defines HRQL as “..a broad multidimensional concept that usually includes self-reported measures of physical and mental health”. In 2009, the US Food and Drug Administration proposed the umbrella term *patient-reported outcomes* (PROs), defined as:

*“..a measurement of any aspect of a patient’s health status that comes directly from the patient (i.e., without the interpretation of the patient’s responses by a physician or anyone else)”*.

The objective of Valderas et al.<sup>87</sup> was to develop a classification system for PRO measures based on a valid conceptual model, as described in the KQ2 section and illustrated in Figure 4.

#### EGAPP Outcomes of Interest for Evaluation of Genetic Tests<sup>80</sup>

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (EWG) commissions evidence-based reviews and develops recommendations that inform decision-making related to implementation of genetic tests.<sup>138</sup> The identification and appropriate weighting of health outcomes relevant to the test under review is a critical component of this process. Long-term health outcomes (e.g., morbidity and mortality) remain central, though it is clear that the studies necessary to document these outcomes can be challenging to conduct. When considering the broader impacts of genetic tests on individuals, families and society, psychosocial outcomes are often important, though the EWG notes that their systematic evaluation challenges traditional methods of review. However, incorporating these types of outcomes may be necessary to provide balanced and complete information on potential benefits and harms of testing and subsequent interventions.

The EWG’s process for organizing the various outcomes that may relate to testing is a modification of a model proposed by Tatsioni et al.<sup>140</sup> The EWG selected four domains: *diagnostic and prognostic thinking, therapeutic choice, patient impact, and familial and social impact*. Their rationale was that:

*“These domains represent a sequential flow of the test result from its initial impact on the knowledge and attitudes of the patient and clinician, through the subsequent impact on health, to the eventual impact on society more broadly.”<sup>80</sup>*



**Table 6. Modified EGAPP disease-specific outcomes matrix<sup>138</sup>**

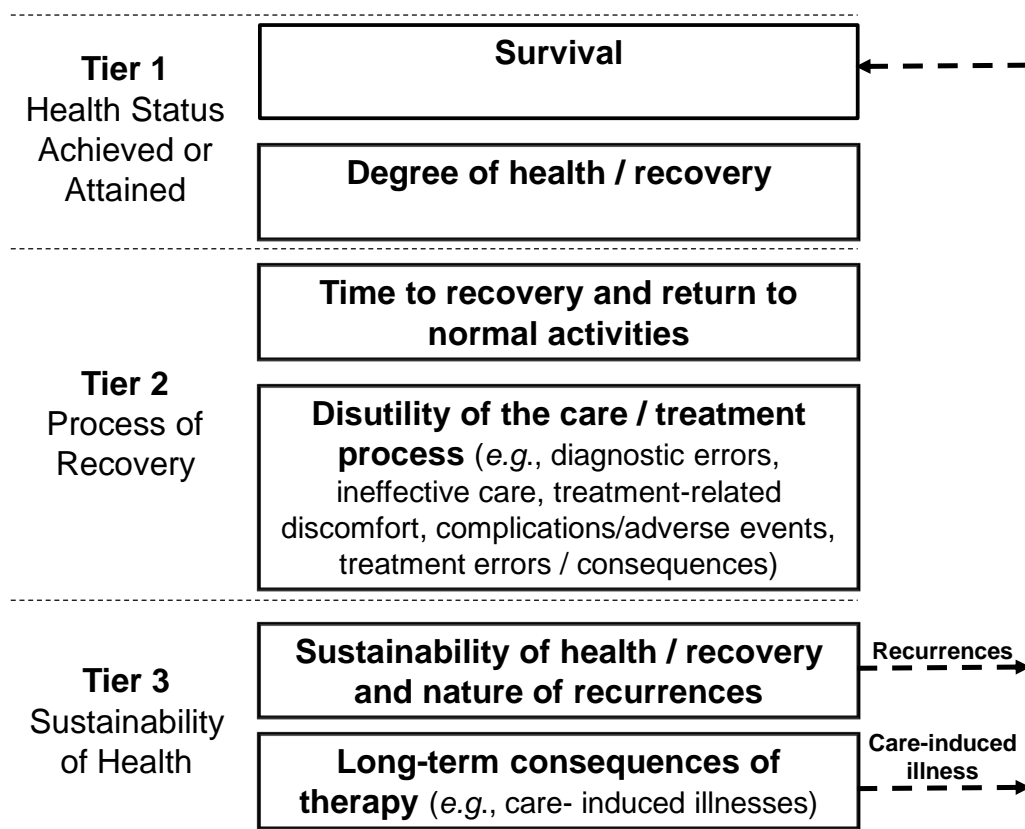
Outcomes	Outcome type		Outcome relevance		
	Patient	Physician	Individual	Family	Society
<i>Long-term health outcomes</i>					
e.g., morbidity, mortality, function					
<i>Short-term health outcomes</i>					
e.g., decision-making, adverse drug reaction					
<i>Patient-reported outcomes</i>					
e.g., function, HRQL, acceptability					

Examples of the different types of health-related outcomes can be found in Table B9 (Appendix B). This particular stratification process appears to work well for planning systematic reviews, but is perhaps less helpful for developing an outcomes framework for clinical genetics services. What may be helpful, however, is their concept of a disease-specific outcomes matrix (Table 6). Use of this matrix includes development of a list of outcomes (e.g., long-term, short-term, patient-reported, other) specific to the disease, followed by consideration of whether the outcome is measured by the physician, patient or both, and to whom the outcomes are relevant. A disease-specific example (non-psychotic depression treated with selective serotonin reuptake inhibitors) can be found in Table B10 (Appendix B).

Porter Outcome Measures Hierarchy<sup>10,17</sup>

Porter provided background and rationale for his proposed outcome measures hierarchy. Effective health outcomes measurement must include more than survival, as “survival alone omits many factors of great significance to patients.” He emphasizes his contention that health outcome measures must be considered distinct from measures of the care process, the interventions intended to achieve the health results, or the biologic indicators that are predictors of results. As examples, he notes that “..discomfort, timelines, and complications of care are outcomes, not process measures, because they relate directly to the health status of the patient.” He classifies patient satisfaction with care as a process measure, but patient satisfaction with health as an outcome measure.

Figure 8 illustrates the components of the Porter health outcomes hierarchy. There are three tiers. He designates the top tier, *Health status achieved or attained*, as generally the most important, with lower tier outcomes involving “..a progression of results contingent on success at the higher tiers.” Tier 2 is the *Process of recovery*, and Tier 3 the *Sustainability of health*. Each tier contains two levels, designated *outcome dimensions*. Each level or outcome dimension is measured using one or more specific *metrics* or *outcome measures*, intended to capture specific elements of patient health. Health outcome measures were described as specific to disease/condition or populations (e.g., primary care patients). Porter recommends beginning the process with at least one outcome dimension in each tier, and ideally one at each level.



**Figure 8. Porter Outcomes Measures Hierarchy<sup>5,10,17</sup>**

### Characteristics of the Outcome Hierarchies

*“Outcome in the world of health care has..until relatively recently focused upon mortality and life expectancy...a rather limiting understanding as outcome...embraces specific technical measures, functional and psychological measurements of the patient’s health state.”<sup>103</sup>*

Table 7 provides a cross-walk of outcomes from the six outcome hierarchies described above<sup>17,59,80,84,87,126</sup>, with outcome measures categorized as:

- health outcomes;
- intermediate or shorter-term outcomes or health indicators;
- HRQL / PROs;
- other PROs;
- process measures; or
- structure measures.

Two limitations of the table are some overlaps in measures between different categories, and the reviewer’s subjective assignment when categorization was not specifically indicated by the author.

**Table 7. Sample comparison of outcome measures.**

	<b>Porter, 2010<sup>10,17</sup></b> <b>Outcome Measures Hierarchy</b>	<b>Botkin, 2010<sup>80</sup></b> <b>Types of health-related outcomes</b>	<b>Silvey, 2009<sup>126</sup></b> <b>Genetics Services Outcomes Menu</b>	<b>Valderas, 2009<sup>87</sup></b> <b>PROs Classification System</b>	<b>Payne, 2008<sup>59</sup></b> <b>Validated Outcome Measures</b>	<b>Wang, 2004<sup>84</sup></b> <b>Framework for Evaluating Genetic Svcs</b>
<b>Health Outcomes</b>	<b>Tier 1</b> Health status achieved/ retained Survival Health recovery	<b>Patient outcome impact</b> Mortality, morbidity Incidence/severity of adverse outcomes Change in Tx response  Termination of pregnancy Prenatal interventions	Symptoms prevented Need for urgent/emergency care decreases Diagnosis obtained for patients with genetic conditions		Reproductive decisions	Morbidity Mortality Reproductive decisions
	<b>Tier 2</b> Process of recovery Time to recovery/normal activities Disutility of care/treatment					
	<b>Tier 3</b> Sustainability of Health Sustainability of health/recovery; recurrences Long-term consequences of therapy					
<b>Intermed Outcome/Health Ind<sup>e</sup></b>	Example HbA1c	Response to therapy Change in preventive or therapeutic strategy	Improved diet/nutrition Symptoms detected early		Diagnostic accuracy	Screening adherence
<b>PROs HRQL</b>	HRQL	HRQL Disabilities perspective	Optimal psychosocial health Optimal physical health Daily functioning optimal	Symptoms Functional status Health perceptions HRQL	Decision making	Treatment decisions Quality of life Decision making /informed choice

<b>Other PROs</b>	Patient satisfaction	Patient satisfaction with services Ending diagnostic odyssey Knowledge of prognosis/ planning Changes in family dynamics Change in sense of control Distress Stigmatization/ discrimination		Patient satisfaction with care Other health-related constructs – Disadvantage Resilience Environmental	Knowledge Risk comprehension Perceived personal control Psychological impact Satisfaction Expectations Adaptation Self-esteem Worry	Knowledge Risk comprehension Perceived control Satisfaction w/ care and information
<b>Process Measures</b>	Compliance	<b>Adherence to therapeutic regimen</b> Healthy behaviors Health care utilization by family members Health disparities				Satisfaction w/ communication w/ counselor Adherence to screening/therapy Lifestyle behaviors
<b>Structure Measures</b>						Genetic counselor competencies

Tx = therapy; HbA1c = hemoglobin A1c; HRQL = health related quality of life

Note some overlaps between categories, particularly between HRQL / PROs, other PROs and process measures. Note also that this table represents identified outcomes hierarchies with relevance to the review, not a comprehensive review of disease-specific outcomes development based on research or public health surveillance processes. Figure 9 provides a visual representation of the range of outcome measures addressed by the outcomes hierarchies and the lack of clear distinctions in this continuum of outcomes.

The Porter NEJM publication<sup>17</sup> and on-line supplementary materials<sup>5,10</sup> have generated both interest and controversy; even, it appears, within the Committee. Porter has been lauded for his “detailed focus on outcomes” (Tilburt et al., Cohen<sup>141</sup>), his innovative “model of multidimensional, longitudinal outcome metrics” (Stuart & Chernof<sup>141</sup>) and for creating a “context for improvement”<sup>76</sup>. He has also been criticized for a “payer-centered rather than a patient-centered perspective” (*i.e.*, an outcomes hierarchy that does not take into account patient perspectives and outcomes of interest to patients), and his use of the term “functional status” (Tilburt et al., Cohen, Stuart & Chernof<sup>141</sup>).

Porter<sup>141</sup> responded that:

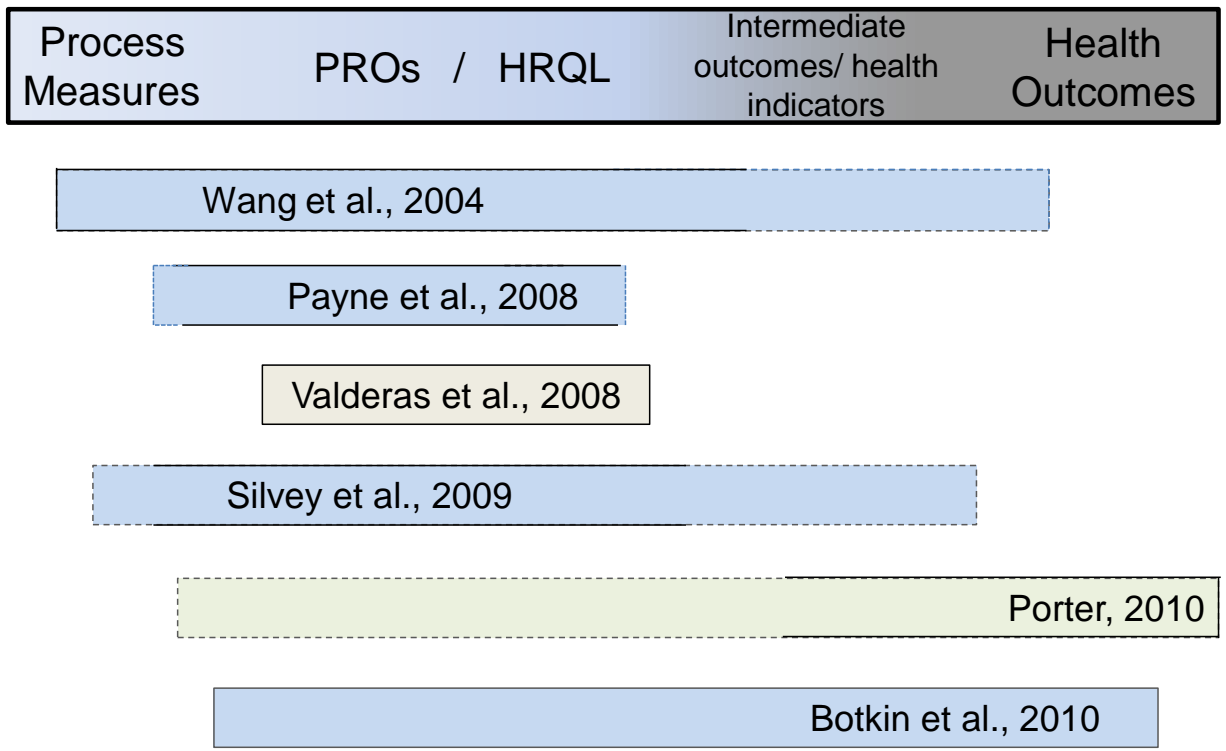
- the “outcome hierarchy is inherently patient-centered”, because it describes actual health outcomes of patients rather than provider perspective through process measures;
- as illustrated in his model for measuring value (top of Figure 5), family participation and support was considered integral to the “initial patient conditions that influence health outcomes, not the health outcomes themselves”<sup>141</sup>; and
- “functional status is essential to patient-centered measurement and the hierarchy”, proposing development of disorder-specific functional status metrics, rather than using standardized scales.

Another critique was the TEP’s observation that Porter emphasized the importance of quantifying costs in order to obtain an estimate of value, but did not actually integrate cost into the value model or the outcomes hierarchy.

Considering the outcome hierarchies as a group, it would appear that all have strengths and weaknesses. Valderas et al. focused solely on PROs. While acknowledging the need for PROs and HRQL in his model<sup>5</sup> and web supplement papers<sup>5,10</sup>, Porter focused on the narrow view of health outcomes as selected and measured mainly by clinicians and researchers. Silvey, Payne and Wang touched on health outcomes but were somewhat more focused on PROs and process outcomes. Botkin et al. took an overarching approach that included several categories of outcomes. Many other researchers and policy developers are working to define, classify and effectively measure PROs, HRQL and other outcomes of interest to patients (see KQ5).

### **Process and Structure Measures**

A second approach to assessment of health care quality is to examine the *process of care* itself rather than its health outcomes. The best process measures are supported by evidence and tied to processes of care over which the health care system has some control.<sup>4</sup> It is generally



**Figure 9. Focus of outcome measures hierarchies.**  
 Dashed lines represent some coverage but minor focus. Those with darker shading were developed to address genetic services.

PRO = Patient reported outcomes; HRQL = health related quality of life

thought that the estimates of quality obtained using process measures “.. are less stable and less final than those that derive from the measurement of outcomes.”<sup>85</sup> As previously noted, Porter<sup>17</sup> states this view much more strongly:

*“Process measurement, though a useful internal strategy for health care institutions, is not a substitute for measuring outcomes. There is no substitute for measuring actual outcomes, whose principal purpose is not comparing providers but enabling innovations in care.”*

The focus on process measurement is not particularly surprising. Tracking process measures is “..often less controversial,..much easier to measure than outcomes, and..can be measured in the short term.”<sup>5</sup> Resistance to, or lack of resources for, implementing outcome measures has: *“..pushed policy groups to measure processes, a practice that exacerbates the micromanagement of medical practice. Measuring processes rather than outcomes is essentially measuring inputs instead of outputs. Given highly similar inputs, different teams will still achieve varying results...Process compliance does not guarantee better outcomes.”*<sup>92</sup>

McAllister et al.<sup>44</sup> note that process has been defined as “..anything in the individual’s utility function (strategy for goal attainment) other than the final health outcome that the intervention affects”. Defined in this way, process could include a measure such as “access to the intervention” that could have a significant impact on patient outcomes. The authors propose five process measures that may contribute to improved patient outcomes:

- local and accessible services;
- ongoing access and yearly follow-up;
- coordinated and tailored family care;
- quality of the (health care provider – patient) relationship; and
- time to talk.

A third approach to assessment is to study the settings in which health care takes place.<sup>85</sup> Donabedian defined this concept as *structure*, and further defined the settings as including the facilities, qualified staff, and administrative / fiscal organization that support medical care.<sup>85</sup> In the literature, process measures are sometimes confused or confounded not only with outcome measures, but also with structural measures.<sup>17</sup>

In 2009, Zellerino et al.<sup>19</sup> reported the results of a comprehensive literature search and international survey aimed at identifying and prioritizing a broad range of process and structure measures on dimensions of performance in clinical genetics. Potential indicators were selected based on six criteria, including validity, feasibility and sensitivity (*i.e.*, ability to detect change). Multiple perspectives on the appropriateness and practicality of the 24 selected indicators were sought through multi-national and US surveys. Based on survey results, three of the top five indicators were measures of process (urgent referral, follow-up arrangements, collegial communication) and two were patient-centeredness outcomes (respect given, patient questions answered). A working group composed of representatives of genetics regional collaborative centers and the ACMG Quality Special Interest Group proposed five indicators (process

measures) for further pilot study (no subsequent reports were identified). These measures were:

- Referral communication
- Follow-up plan
- Appointment availability – routine
- Appointment availability - referral
- Patient Satisfaction Survey

### **Clinical genetics outcome measures and perspectives identified in the general search**

*"...outcome measurement is difficult because the definition of "success" for genetics services is rarely stated explicitly."<sup>84</sup>*

Gray et al.<sup>63</sup> observed in 2009 that: "Clinical genetics is a discipline undergoing huge changes, driven by rapid scientific discovery. It benefits from a committed, innovative, and knowledgeable workforce." The clinical genetics community, however, faces a challenge in being able to describe the services it provides and to measure their quality."

- Chou et al.<sup>56</sup> reported in 2009 that: "To date, published work has primarily focused on structure and process, and evidence related to outcomes is severely lacking." Their systematic review on outcomes measurement in clinical genetic services identified 29 studies investigating structure outcomes (Donabedian model), identified as:
  - Access to care (n=1)
  - Health information and databases (n=4)
  - Health information technology (n=3)
  - Medical home and organization of services (n=2)
  - Workforces education and training (n=9)
  - Program components and development (n=10)

They identified 19 studies reporting on process outcomes, identified as:

- Patient-provider interaction (n=7)
- Care provision, coordination and management (n=6)
- Quality assurance mechanisms (n=6)

They identified only seven studies related to outcomes. One of the seven was a systematic review looking for studies of both genetic and non-genetic outcomes. The three non-genetic-specific outcomes would best be described as process measures. The three genetic-specific studies reported on health outcomes (cost-effectiveness of *BRCA1/2* testing, colonoscopy surveillance for Lynch syndrome, morbidity/mortality in hereditary hemochromatosis).<sup>56</sup>

- Payne et al.<sup>48</sup> used a Delphi survey to compare healthcare professional and patient views on outcome measures for clinical genetic services. They found that (health or health-related outcomes are italicized):



- Health care professionals ranked the outcome measures as: 1) *decision making*; 2) satisfaction; 3) knowledge of the genetic condition; 4) coping; 5) *accuracy of diagnosis*; 6) perceived personal control; 7) risk perception; 8) meeting expectations; and 9) *quality of life*.
- Patients ranked the outcomes measures as: 1) satisfaction; 2) accuracy of test; 3) *accuracy of diagnosis*; 4) knowledge of the genetic condition; 5) perceived personal control; 6) *decision making*; 7) risk perception; 8) coping; 9) meeting of expectations; 10) *quality of life*; and 11) family environment.

Only short-term outcomes (e.g., decision-making, accuracy of diagnosis) received a high rank from health care professionals or patients. *Health status* did not have a high rank in either group, though health care professionals considered *health status* to be more important (P <0.001) than patients.

- In a 2008 systematic review of health outcomes for common chronic diseases with a genetic component, Scheuner et al.<sup>60</sup> identified four studies of genetic/genomic health services that addressed “clinical outcomes”:

Pre-operative warfarin therapy	Effect of genotyping on INR results
Weight management clinic	Non-randomized comparison of nutrigenomic test results on weight loss
Pre/post testing	Effect of positive <i>BRCA1/2</i> results on risk-reducing clinical decision-making and participation in screening
Semi-structured interviews	Effect of <i>BRCA1/2</i> variant of unknown significance results on result interpretation and effects on life domains

### **Clinical genetics disease specific outcome measures identified through targeted searches**

In responding to the TEP’s request for additional disease-specific research, it was again not within the scope to prepare a comprehensive summary of primary studies. Targeted searches were conducted in MEDLINE for the following topics:

- Phenylketonuria – The search [(“phenylketonuria” OR “PKU”) AND (“outcomes” or “clinical outcomes” or “long-term outcomes” or “health outcomes”)]; limited to English, reviews, systematic reviews, meta-analyses] identified only one relevant article out of 13.<sup>142</sup> Waisbren et al. conducted a systematic review of 228 published trials that included Phe level and neurological and dietary compliance outcome measures. Neurological measures included IQ, brain MRI, and neurophysiological function measures (e.g., attention, memory, organization, behavior regulation and academic achievement), and dietary measures (e.g., blood Phe levels by age). Meta-analyses were performed on subsets of subjects, defined by type of disease (e.g., classic, mild) and other variables. Results confirmed a significant correlation between blood Phe levels and IQ. Additional information on outcomes was not provided.

- Newborn Screening – The search [(“neonatal screening”[Mesh] AND “outcome assessment (health care)”[All Fields]); limits English and years 2006-2011] identified 33 articles, six of which were part of a *Genetics in Medicine* December 2010 Supplement on long-term follow-up of newborn screening patients (all of the articles in this supplement were subsequently reviewed). Most articles described the processes and information systems being developed to support the “..clinical and public health activities involved in long-term follow-up of children with conditions identified by newborn dried bloodspot screening.”<sup>134,143</sup> However, Feuchtbaum et al.<sup>144</sup> provided preliminary findings for short- and long-term newborn screening follow-up of children identified with metabolic disorders in the California system. For the majority of children, ongoing care was assessed through age 5 years. The outcome measure framework reported included (quoted):

Short-term follow-up (by disorder)

Median days from DOB to initiation of follow-up (FU) care  
 Median days from DOB to diagnosis or resolution  
 Number lost to FU  
 Number of newborn deaths before FU  
 Number of parents refusing FU

Long-term follow-up (by age of child)

FU status by year  
 Service utilization in each year (e.g., genetic counseling, health education, laboratory tests, nutrition advice, physical exam, social services)  
 Mortality related to metabolic disorder  
 Asymptomatic or symptoms  
 Developmental delays (mild, moderate or severe)  
     Speech/language  
     Physical growth  
     Mental/cognitive  
     Gross and fine motor skills  
 Age appropriate development in the above categories  
 Loss of skills from previous year  
 Hospitalizations  
 Treatment types (e.g., medical foods/supplements, medications, enteral feeding)  
 Emergency room visits related to the metabolic disorder  
 Provider assessment of the overall health of the child

- Lysosomal storage disorders (LSDs) - The search [(“Outcome Assessment (health care)” AND (“genetic diseases, inborn”[Mesh] OR “genetic counseling”); limits English and years 2006-2011] identified 361 articles. Two of the most recent articles<sup>145,146</sup>, one a review and one a primary study of psychological outcomes, were selected as representative articles. The 2011 review<sup>145</sup> reported on the usefulness of disease registries in studying diseases affecting very small patient populations such as LSDs. Data from registries can also provide information on natural history, measure

effectiveness of treatment, and monitor developmental health outcomes. The overall framework for long-term clinical effectiveness outcomes for interventions such as enzyme replacement therapy included:

- Safety, including reporting of adverse events
- Treatment efficacy/effectiveness
- Cognitive development
- Developmental progression, including height, weight and reproductive development
- HRQL
- Functional outcomes
- Impact on siblings
- Genotype-phenotype associations

Disease-specific outcomes were discussed for individual LSDs. For example, large analyses of longitudinal data on adults and children with Gaucher disease have provided data on natural history and long-term outcomes. Clinical parameters studied in Gaucher disease type 1 treated with enzyme replacement therapy included height, liver and spleen volumes, bone mineral density (osteopenia), hematologic abnormalities such as anemia, and progressive morbidity and mortality.<sup>145,146</sup>

A primary study<sup>146</sup> investigated the “distinct psychological complications” associated with the “extensive, painful and even life-threatening” clinical manifestations of Gaucher disease. Psychosocial measures included coping with the diagnosis, the “effects of pain and fatigue on job, career and recreational activities” and insurance concerns.

### **Outcomes of genetic counseling**

*“Most studies of outcomes of genetic counseling have focused on client knowledge, reproductive plans and behavior, or satisfaction. Other measures of the “value” of genetic counseling are needed to guide research assessing the impact of genetic counseling on individuals and populations, as well as to improve the process of providing care.”*

National Society of Genetic Counselors, 2006<sup>37</sup>

*“Genetic counseling should be assessed not only in terms of patients’ knowledge of the disorder, its significance for them (and their families) and of the preventive and therapeutic actions open to them but, more importantly, in terms of their adjustment to this knowledge. These are psychological outcomes.”*

Fryer et al., 1998<sup>61</sup>

Early outcomes of interest in genetic counseling studies included post-counseling patient knowledge, risk comprehension and changes in risk perception, reproductive plans and post-counseling behavior, psychological distress, patient satisfaction with the counseling experience, as well as the effectiveness of informational materials (e.g., brochures, videos) used in conjunction with providers or genetic counselors.<sup>37,53,84</sup> Wang et al. listed the most commonly

investigated criteria as knowledge acquisition, risk comprehension, psychological distress, patient satisfaction, and reproductive decision-making.<sup>84</sup> The authors noted that this represents a small number of outcomes when considering the many stated goals of genetic counseling, and proposed other areas in which to develop outcome measures:

- perceived personal control (PPC);
- meeting patient expectations;
- genetic counseling processes (e.g., competencies, communication, therapeutic approaches)
- informed decision-making and decision processes (i.e., ensuring that “..the decision is based on relevant, high quality information, reflects the values of the person making the decision, and is behaviorally implemented”).<sup>84</sup>

In 2007, Kasparian et al.<sup>104</sup> described and further evaluated outcome measurement scales used at that time in genetic counseling outcomes research. They identified 19 instruments that had a published validation study and reliability estimate, including:

- Genetic Counseling Satisfaction Scale (GCSS)
- Perceived Personal Control questionnaire (PPC)
- Decision Evaluation and Regret Scales (DES, DRS)
- Breast cancer genetic counseling knowledge questionnaire (BGKQ)

These and other instruments/scales measure a number of outcome measures among patients counseled, including:

- Knowledge
- Decision-making
- Psychological adjustment
- Coping
- Perceived personal control
- Perceptions of disease risk
- Family communication about genetic risk

Patient background, needs and expectations (BNE) have been shown in many studies to be predictors and modifiers of the genetic counseling process and its outcomes.<sup>37,49</sup> In 2011, a BNE Scale was developed and entered validation.<sup>49</sup> Recent results provide further evidence of the BNE Scale’s validity in characterizing groups of individuals, and support the concept of differential genetic counseling goal setting (and perhaps outcome measures) based on practice subspecialty. Another recent study reported on the development and early validation of a new Genetic Counseling Outcome Scale with 24 questions (GCOS-24) (Table B18, Appendix B) that addresses patient-reported outcome measures (PROMs), such as HRQL, PPC, anxiety, depression, health locus of control and empowerment (see KQ5).<sup>133</sup>

### **Perspectives on clinical genetics health outcomes**

As the design of KQ 4 suggests, outcomes of interest can be viewed from many perspectives. Doerge et al.<sup>74</sup> considered recipients of health care overall, and proposed that outcomes should be considered for:

- individual patients;
- 'high risk' individuals defined by specific indicators;

- target groups for disease-specific initiatives;
- strategic demographic groups of populations that might benefit from public health (or clinical) programs raising awareness of specific disorders;
- the broader community, which may be defined by geography, economics, race/ethnicity, cultural norms, or access to health care.

In general, it seems that this concept applies well to patients and sub-populations of patients and/or the general population who have received, are receiving, or could benefit from, genetic diagnosis and other clinical genetic services. Family members could be included in “target groups” but would seem to merit special mention.

Much has been presented about potential impact on health outcome measures for diagnosed individuals, and some attention paid to family members in several roles (e.g., patient supporters, at risk individuals based on diagnosis of a proband, and information seekers needing to understand their risks and options). Important outcomes for some types of genetic testing relate to impacts on family members that result from one original test.<sup>71</sup> Important questions include whether and how family members are informed of their genetic risk, whether they want to know their risk, and whether they are interested in genetic counseling, clinical evaluation, or genetic testing. Consequently, patient outcomes often include the effects of testing that cascade through the proband’s family.<sup>71</sup> Porter noted that “..family issues (e.g., closeness, communication, relationships) may be more significant than health-related outcomes when evaluating services” for people with heritable conditions.<sup>67</sup>

Interviews of ACMG Quality Assurance Subcommittee members provided a clinical perspective on to two important questions<sup>127</sup>:

*What does establishing a clinical diagnosis contribute to the management of an affected individual?:*

Define prognosis and related risks  
 Intervention is diagnosis dependent  
 Do nothing  
 Early intervention  
 Therapy to stabilize  
 Prevent symptoms  
 Surveillance  
 Access to medical foods  
 Provide ancillary services (support, education)  
 Chemoprevention or other therapy in heritable cancers  
 Minimize stigmatization  
 End diagnostic odyssey  
 Clinical trial eligibility

*What does establishing a clinical diagnosis contribute to the care of the family of an affected individual?:*

Vertical and horizontal family workup  
 Knowledge of disorder/mutation  
 Anticipatory guidance  
 Assessment and understanding of risk  
 Targeted family surveillance and testing  
 Family planning/reproductive options  
 Carrier testing, prenatal diagnosis option for at risk individuals  
 Identify additional mutation-based risks  
 Support group & community resources  
 Allows most informed choices possible

Another feature of clinical genetics is that many “patients” are asymptomatic and healthy, but at risk of developing a disorder or condition, and/or dealing with the concepts of transmitting a condition to their children and potentially communicating news of potential risk to family members. In that sense, the value of genetic diagnosis for individuals and families is inextricably linked.

*“New outcome measures in clinical genetics services need to quantify the degree to which interventions in clinical genetics services provide benefit to patients and their families.”<sup>45</sup>*

## **Experience of existing processes or investigators in developing and validating non-genetic quality indicators and outcome measures**

### National Quality Measures Clearinghouse<sup>8</sup>

NQMC is sponsored by the Agency for Healthcare Research and Quality to support access to evidence-based quality measures for health care providers, payers, health plans and others. NQMC uses the IOM definition of *quality of care* and groups measures of quality of care into seven domains (Table B11, Appendix B). NQMC notes the importance of considering whether the intended use is consistent with the quality measure’s validated use. The NQMC web site currently lists 363 validated quality measures for healthcare *outcomes*, 1,055 for *process*, 25 for *access*, 121 for *structure*, 299 for *patient experience* and 64 for *use of services*.

NQMC provides five questions to assess the validity of proposed quality measures (quoted):

- How strong is the evidence supporting the validity of the quality measure?
- Are all individuals in the denominator equally eligible for inclusion in the numerator (valid measures exclude individuals who should not receive the indicated care or are not at risk for the outcome)?
- Is the measure result under control of those whom the measure evaluates?
- How well do the measure specifications capture the event that is the subject of the measure?
- Does the measure provide for fair comparisons of the performance of providers, facilities, health plans or geographic areas?

NQMC defines five outcome types:

- Clinical outcome such as mortality, changes in symptoms, HbA1c level
- Adverse outcome such as an injury due to a medical treatment
- Functional status – measure of an individual’s ability to perform normal activities of life
- Health risk state or behavior – where risk is a factor for a clinically diagnosable condition (not the diagnosed condition itself)
- Proxy for outcome – process of care (e.g., hospital admission) used as an indicator of health status
- Quality of life measure - health-related quality of life (HRQL) related to aspects of a person's overall well-being that are affected by health status or health care

Organisation for Economic Co-Operation and Development (OECD) Health Policy Studies on Improving Value in Health Care: Measuring Quality<sup>147</sup>

The OECD's Health Care Quality Indicators (HCQI) Project was initiated in 2002 to provide "a conceptual framework and methodological basis to provide the required information on quality" in health care. This project includes representation from Europe / European Commission, Australia, Asia, and North America (including the U.S.). Recommendations in their 2010 report included: 1) exploiting "the potential of national registries and administrative databases" to measure quality; 2) "implementing the comprehensive use of electronic health records"; 3) "establishing national systems to collect longitudinal information on patient experience"; 4) ensuring consistency and linkage of quality measurement processes with health policies and monitoring; and 5) seeking examples of good quality improvement practice from other countries to determine if the knowledge can have local application. They identified the main information sources of for population-based quality indicators as birth and death statistics (mortality data), specific registries (e.g., cancer, specific diseases, specific specialties), administrative databases, electronic health records, and population and patient-based surveys. They also developed seven principles for establishing national systems for capturing patient experiences in health care, and seven principles to consider when choosing and implementing quality indicators related to health outcomes. The latter include: 1) careful choice of indicators based on a clear definition of intended purpose (e.g., can find meaningful differences, provide signals offering clear and actionable response, monitor changes over time); 2) "clear signaling" regarding validity of outcome measures (e.g., mortality outcomes are useful but do differences really result from the intervention of interest); 3) "trustworthiness" of the quality of data and robustness of methods used to collect the data; 4) wariness about single indicators or single health care setting, and the need to consider context; 5) "a chain is only as strong as its weakest link" in terms of summary scores; 6) without proper analysis (e.g., confidence estimates), an observation can be due to chance; and 7) wariness of unintended consequences, "gaming" or "outright cheating" with regard to information reporting for quality improvement. This report emphasizes the reality that all health care systems today face similar challenges in systematically addressing health care quality issues. Though they acknowledge that there is no "one size fits all" solution, experience gained locally and internationally often points in similar directions, and may be useful to consider.

United Kingdom (UK) Quality Outcomes Framework<sup>79,148-151</sup>

The national Quality and Outcomes Framework (QOF) was introduced in the UK in 2004. Like the US NQMC, the objective of the QOF is to improve the quality of health care received by patients. However, rather than providing only a publicly available resource, the QOF approach is to offer financial reward to practices based on the quality of care they provide to their patients. Although voluntary, the participation rate is high. The 8,305 practices in England included in the 2009/10 QOF report accounted for 99.7% of registered patients in England.

The QOF contains four *domains*: *Clinical, Organizational, Patient Experience* and *Additional Services*. Each domain comprises a set of achievement measures, termed *indicators*; content and number of indicators in each domain are detailed in Table B12 (Appendix B). Table B13

(Appendix B) describes the development and ideal characteristics of QOF quality indicators.<sup>9,79</sup> In 2009-2010, achievement was measured against 134 QOF indicators. However, most indicators were measures of structure or process, and have no direct therapeutic effect.<sup>9</sup> Journal editorials in the UK regularly debate the pros and cons of this program, and its potential versus real contributions to improving quality of health care. An important limitation is that only a small subset of possible indicators has been addressed.<sup>151</sup>

#### American College of Cardiology/American Heart Association (ACC/AHA)

*"The foundation of efforts to improve (health) care is predicated on measurement."*  
Spertus et al., 2005<sup>7</sup>

In 1999, the ACC/AHA conducted the First Scientific Forum on Assessment of Quality of Care and Outcomes Research in Cardiovascular Disease and Stroke.<sup>152</sup> Themes discussed at this included:

- Linking development of guidelines with development of performance measures or quality indicators, as both are related to the same body of evidence
- Considering methodological challenges in quantifying quality (e.g., data quality, time frames for tracking outcomes, risk adjustment, developing conceptual frameworks, selecting structural, process and outcome measures)
- Developing research priorities

The ACC/AHA continued this process and have developed a strategy to facilitate improvement in the quality of cardiovascular care based on measurement.<sup>6,7</sup> The first step in the project involved synthesis of available evidence to develop clinical practice guidelines.<sup>7</sup> The second was to develop a plan for constructing a measurement set, assessing the feasibility and reliability of data collection and implementing measurements of physician performance. In some cases, the evidence supporting a process or structure measure is sufficiently strong that failure to perform the actions can reduce the likelihood of an optimal outcome. Therefore, measuring adherence to such actions can serve as a direct measure of quality of care (or some component of quality) and a basis for quality improvement.

The process begins with the definition of the disorder of interest, the target population and the focus of the performance measures to be chosen. An example might be prevention of thromboembolism in patients aged 18 or older with a diagnosis of nonvalvular atrial fibrillation (AF) or atrial flutter.<sup>6</sup> The next step would be to determine the *dimensions of care* that should be targeted. An example of care dimensions for a heart condition in ambulatory care might be: patient diagnosis, patient education, patient treatment, patient self-management, monitoring patient health status and response to therapy.<sup>7</sup> A sample framework for defining the target population, phases of and a plan for performance measure development and exclusion criteria for performance measures can be found in Tables B14, B15, B16 and B17 (Appendix B).<sup>6,7</sup>

Continuing the example above, a set of three performance measures for prevention of thromboembolism in AF were selected from eight candidate measures.<sup>6</sup>



Dimension of Care→	Diagnostics	Patient education	Treatment	Self-management	Monitoring status
<b>Performance measure</b>					
Assessment of thrombo-embolic risk factors	●				
Chronic anticoagulation therapy			●		
Monthly INR measurement			●		

Estes et al.<sup>6</sup> also provided a summary of ACC/AHA attributes of good performance measures:

- Useful to improve patient outcomes: evidence-based, interpretable, actionable
- Measure design: valid, reliable, numerator/denominator precisely defined
- Measure implementation: feasible effort, cost and time for collection
- Overall assessment documented

The cardiac disorder-specific ACC/AHA committees (e.g., chronic heart failure, nonvalvular atrial fibrillation and atrial flutter, myocardial infarction) published at least 18 articles on the development and use of performance measures between 2005 and 2008. More recently, studies have appeared assessing the impact of these performance measures. For example, a 2010 systematic review identified 11 original US studies and a literature review that assessed the association between ACC/AHA performance measures for patients from an inpatient setting with chronic heart failure and the patients' clinical outcomes (hospital readmissions, short-term mortality).<sup>58</sup> They concluded that "...an increase in compliance with the heart failure performance measures leads to a consistent positive impact on patient outcomes although the strength, magnitude and significance of this effect is variable across the individual performance indicators."<sup>58</sup>

The QI program developed through this process is called the *Cardiology Practice Improvement Pathway* (CPIP). [CardioSource.org/CPIP](http://www.cardiosource.org/Science-And-Quality/Quality-Programs/CPIP.aspx?w_nav=Search&WT.oss=CPIP&WT.oss_r=8&) ([http://www.cardiosource.org/Science-And-Quality/Quality-Programs/CPIP.aspx?w\\_nav=Search&WT.oss=CPIP&WT.oss\\_r=8&](http://www.cardiosource.org/Science-And-Quality/Quality-Programs/CPIP.aspx?w_nav=Search&WT.oss=CPIP&WT.oss_r=8&)).

Information available from this web page includes the detailed CPIP Practice Guide, Volume 1, Stage A: *Assessing your Practice Performance*.

Dept. of Orthopaedic Surgery, Washington University School of Medicine, St. Louis, MO

Identified as a published review on *Shoulder Outcome Measures*<sup>70</sup> this article was selected as another example of development and application of performance measures by individual specialties and institutions. The authors note that outcomes of shoulder injuries have been evaluated using rating scales and scoring systems for many years. Of course, shoulder problems in general can have more complex etiologies. Orthopedic outcome measures generally come from two broad categories, general health and disease- or joint-specific. Having

had extensive review in the *Journal of the American Academy of Orthopaedic Surgeons*, The Medical Outcomes Study 36-Item Short Form (SF-36) is the most commonly used general health outcomes measure among orthopedists. Other measures are specific to the disease and the affected joint. Of the more than 30 shoulder outcome measures described, nine have been extensively validated, and are reviewed in detail in this report. Of more interest for the purposes of the current review is their approach. In their view, a patient evaluation should take a broad view and include:

- a general outcome measure (e.g., SF-36) “..to allow for comparison with other musculoskeletal and systemic diseases.”
- a shoulder outcome measure validated for the specific disease or condition and/or “..a general cross-sectional shoulder-specific measure (that) allows comparison for different diagnoses.”
- a measure of shoulder activity.

It is not indicated in this article whether or how the results and scores of these measures are aggregated. It may be left to the physician’s judgment to determine how the different measures are considered and weighted.

Porter<sup>5,17</sup> suggests that health outcomes measures selected should:

- be important to the patient;
- be variable enough to require focus and improvement;
- occur frequently enough to justify the costs of measurement, though rare outcomes may need to be measured;
- be practical and feasible;
- best capture the particular outcome from the perspective of the patient and medical science;
- include standard and tested measures to improve validity and enable comparison across providers;
- include both short and longer-term health outcomes;
- cover a time period for data collection that encompasses the ultimate results of care;
- provide sufficient measurement of risk factors or initial conditions to allow for risk adjustment;
- minimize ambiguity and judgment in scoring or interpreting, to ensure accuracy and consistency;
- utilize patient surveys to capture “..outcomes such as functional status and discomfort that reflect patients’ realities and are difficult for outside parties to measure...standardized scales such as the SF-36 or the Beck Depression Index are preferable when available”; and
- include practical considerations, “such as the availability of data and cost of information gathering, ..and number and duration of measurement periods chosen.” He notes that billing data is easier to collect than other data (e.g., from chart reviews), “..so billing data can be the place to start as information systems are improved.”

## Suggested sources for data collection

Methods used to collect data on clinical outcomes include intervention studies (e.g., RCTs, uncontrolled trials), systematic reviews of studies, economic evaluations, and qualitative studies that include survey research.<sup>36</sup> Collection of such data in the absence of research funding is challenging and can strain budgets.

A single article by Garrison et al.<sup>78</sup>, *Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report*, addressed potential data sources that appear applicable to both research and clinical practice. ISPOR is the International Society for Pharmacoeconomics and Outcomes Research. Sources of real world (RW) data include:

- “Registries are prospective, observational cohort studies of patients who have a particular disease and/or are receiving a particular treatment or intervention. Registries involve prospective data collection of clinical, economic, and PRO information.”<sup>78</sup>
  - Registries “..increasingly relying on real-time data capture...typically include a larger and more diverse group of patients than RCTs. ...better reflect RW patients, management practices, and outcomes.”
  - “Patients are often followed over a longer time frame, allowing for an assessment of longer-term outcomes.(with)..few, if any, required visits, evaluations, or procedures. ...treatment patterns reflect everyday clinical decision-making.”
- “Administrative data (typically retrospective or real-time, if possible) are collected primarily for reimbursement, but contain some clinical diagnosis and procedure use with detailed information on charges.”<sup>78</sup>
  - “Claims databases lend themselves to retrospective longitudinal and cross-sectional analyses of clinical and economic outcomes at patient, group, or population levels. Such analyses can be performed at low overall cost and in a short period of time.”
  - “Given the sheer size of claims databases, researchers can identify outcomes of patients with rare events more easily, assess economic impact of various interventions, and gain insight into possible association between interventions and outcomes.”
  - *However* - “Beyond challenges posed by privacy issues, the validity of retrospective claims database analyses has been challenged on several fronts: data quality (missing data, coding errors—whether random or ‘intended’—and the lack of comprehensive data across health care settings); the lack of, or very limited, clinical information on inpatient stays, health outcomes, health status, and symptoms; limited validation; absence of a population denominator; and the lack of distinction between costs and charges.”<sup>78</sup>
  - Considering validation of administrative or claims data:
    - In 2010, Omoto et al.<sup>47</sup> reported on validated measures of functional outcome of lumbar spinal surgery, comparing commonly used outcomes information from an administrative database (e.g., documented imaging and reoperation)

to validated clinical functional outcomes measures. They found no significant relationship between the occurrence of imaging or reoperation and subsequent changes in functional outcome at one or two years post-surgery. Their conclusion: *“Although it may be tempting to consider administrative database outcome measures as proxies for poor functional outcome, we cannot conclude that a significant relationship exists between the occurrence of (imaging) or reoperation and changes in functional outcome.”*

- Krumholz et al.<sup>75</sup> reported a successful proxy measure. Estimates of hospital-level risk-adjusted mortality rates from the claims data-based model were strongly correlated with the estimates from the model based on medical record data. They emphasized that *an attempt should be made to validate “..models using administrative data..against models based on medical data.”*
- “Health surveys... collect descriptions of health status and well-being, healthcare utilization, treatment patterns, and health-care expenditures from patients, providers, or individuals in the general population.”<sup>78</sup>
  - “.. typically information on representative individuals are methodologically rigorous...can provide information about all members of the target population, not just those who are participating in a given RCT, or members of a particular health plan... generalizability of treatments and their impacts and about use of and expenditures for health services.....
  - *However* – “ major limitation...are subject to issues of subjectivity and recall bias.”
- “Electronic health records (EHRs) (and other technologies capturing real-time clinical treatment and outcomes) are important sources for RW data for a wide range of clinical settings throughout the world.”<sup>78</sup>
  - “The expansion of electronic data capture is essentially lowering the cost of the medical chart reviews that have been widely used in the past.”

Benefits of real world data include: the provision of “..estimates of effectiveness rather than efficacy in a variety of typical practice settings; a more diverse and representative patient population; a broader range of outcomes (e.g., PROs, HRQL, symptoms); and handles situations for which RCT is not feasible or when there is urgency.” Limitations of real world data include: “..the potential for bias; requirement substantial resources and linkage of clinical data to claims data; and questions of patient ID and confidentiality.”<sup>78</sup>

### **Proposed barriers that may need to be addressed with regard to outcomes measurement in genetic diagnoses and clinical genetic services**

There are a number of reasons that have been proposed to explain why developing outcome measures in clinical genetics has lagged in general and is behind the small number of systematic efforts in other specialties:

- A major challenge is the lack of defined outcomes.<sup>13</sup>

- Clinical/medical geneticists and genetic counselors constitute a small proportion of medical specialists in the US and have worked largely in the pediatric and prenatal populations until the last decade.<sup>56</sup>
- “Quality measurement in genetics has focused more on patient satisfaction and the presence or absence of program components (e.g., newborn screening, clinical services), rather than effectiveness of care and its impact on intermediate health or health outcomes.”<sup>56</sup>
- There is lack of clarity and agreement on the best outcomes to measure, and traditional measures of health status (EQ-SD or SF36) may not be appropriate because a proportion of genetic conditions can neither be treated nor cured.<sup>43</sup> A similar comment: “New outcome measures in clinical genetics services need to quantify the degree to which interventions in clinical genetics services provide benefit to patients and their families. This is a particular challenge in clinical genetics services because the interventions offered often cannot provide health benefits in the traditional sense of a therapy or cure for the physical problems associated with disease. There are exceptions to this, for example cancer genetics.”<sup>45</sup>
- Clinical genetics interventions often relate to provision of information about a diagnosis, a genetic test result or empiric risk information, with different approaches to outcome measures.<sup>43</sup>
  - “One approach has been to measure patient knowledge or information recall, criticized because of the substantial assumptions that specific items of knowledge are either valued by patients, or contribute to effective decision-making. In effect, these studies are tests of memory and understanding, not evaluations of patient benefit.”
  - “Another approach has been to use generic measures of psychological constructs (anxiety), but these approaches have not been shown to discriminate effectively between different models of service delivery in clinical trials.”
  - “A third, more recent approach is to measure effectiveness of decisions using measures of informed decision-making or decisional conflict. These approaches are limited to evaluating effectiveness of a single decision, and may not be relevant for evaluating clinical genetics services, where outcomes relate to the capacity to make many decisions. Although an important component in assessing healthcare quality, patient satisfaction is not sufficient to capture all the important patient benefits and, furthermore, is influenced by expectations.”
- “Many genetic disorders impact multiple organ systems resulting in a variety of manifestations, which likely cannot be treated with just one intervention.”<sup>86</sup>
- The small numbers of patients with rare diseases<sup>66</sup>
  - For very rare conditions, coding is a major obstacle to retrieving mortality data, as it may be included in larger categories (e.g., ICD-10 E75.2 includes Fabry's, Gaucher,

Krabbe, Niemann-Pick, Farbers syndrome, metachromatic leukodystrophy, and sulfatase deficiency).<sup>66</sup>

- Interpretation of raw outcome data can be misleading in the case of a rare disease. For example, there are only 50 new retinoblastoma patients in the UK each year, among which there are two types – bilateral and unilateral – with different underlying genetics, and four clinical grades relevant to treatment and preserving vision.<sup>66</sup>
- For diagnostic services, the results can be the “correct diagnosis” by definition for rare disorders (e.g., amyloidosis, mitochondrial disorders). Quality in such cases is defined by participation in external quality assurance schemes and laboratory certification/inspection systems.<sup>66</sup>
- Quality measures in clinical genetic services capture only some of the potential patient and family member benefits. Hindrances may include the patient's ability to communicate with at risk family members about that risk and condition, a sense of guilt; difficulty of acceptance and adaptation to the situation, effective use of health and social care systems, and the decision to use reproductive choice.<sup>36</sup>
- Processes for developing specific measures for clinical genetic services have not emerged. Consequently, disease-specific validated measurement scales are lacking; a generic measure may not be sensitive to the type of change that needs to be detected and are expensive (many protected by copyright) and time consuming to administer.<sup>66</sup>

### **General barriers to implementation of outcome measures that may need to be addressed**

An attempt was made to capture specific barriers that were identified in the articles and document narratives:

- Conceptual questions remain<sup>72</sup>:
  - What outcomes matter and to whom - patient, provider, purchaser, insurer or society?
  - How to determine the magnitude of the intervention needed to produce a change in outcome?
  - Who is willing to pay the costs of achieving outcome changes?
  - How to ensure the validity and reliability of measures?
  - How to lessen the burden of collecting data?
  - How to address the need for culturally sensitive tools?
- “Although credible instruments are available to assess these domains, the reliable collection of such data is expensive and not routinely done.”<sup>75</sup>
- “There are rich amounts of observational information in medical records, but virtually none of it is captured in a structured or organized way..(and)...researchers must resort to working with billing codes or other procedure codes in their search for data.”<sup>107</sup>

- Outcomes as important as death are not routinely recorded; functional-status outcomes (e.g., whether a patient with head and-neck cancer can swallow or talk) are buried in free text and are not captured in analyzable form."<sup>76</sup>
- Specific barriers to the development and implementation of measures<sup>83</sup>:
  - Magnitude and speed of change (Note: perhaps particularly applicable to clinical genetics)
  - Growing focus on a multidisciplinary approach based on questions about the usefulness and cost of isolating the impact of any one professional group
  - discipline-specific indicators are rarely automated in clinical information systems (e.g., nursing, genetics).
- Cost of gathering longitudinal outcomes is high due to current fragmented organizational structures, practice patterns and lack of EMR systems.<sup>5</sup>
- “There is scant evidence that one can generalize from the quality of care for one set of symptoms or diseases to the quality of care for another set of symptoms or diseases. It takes skill, time, and money to evaluate the scientific literature, update criteria as science changes, develop and administer valid data-collection instruments, and analyze the results with appropriate methods. It is therefore not surprising that the most widely used system for measuring the performance of health plans, the Health Plan Employer Data and Information Set (HEDIS) is based mostly on readily available administrative data.”<sup>96</sup>
- “There are substantial difficulties in establishing direct causal links between ordering a test and changes in mortality, morbidity, quality of life, and other major patient health outcomes, as a test is likely to be just one of many interventions and environmental and behavioral determinants of patient outcomes.”<sup>111</sup> This may be as true for a health care intervention as for a laboratory test.

In summary for KQ 4, descriptions and comparisons of clinical utility and health outcomes, as well as process and structure measures, have been provided from the literature. Six outcome hierarchies were identified, four of which were developed for clinical genetic services. Narrative descriptions were provided for each, along with a cross-walk table (Table 7) that compares outcome measures categorized as:

- health outcomes;
- intermediate or shorter-term outcomes or health indicators;
- HRQL / PROs;
- other PROs;
- process measures; or
- structure measures.

While not comprehensive, this table provides an overview of the types of outcomes addressed in outcome hierarchies and research studies.

Of the outcomes hierarchies, only two had a primary focus on health outcomes, and one focused solely on PROs. Three touched on health outcomes, but were more focused on PROs and process outcomes. It is important that the strengths and limitations are understood when using these hierarchies, and that the selection of outcome measures is balanced as appropriate by use of other outcome hierarchies or outcomes identified through disease-specific research.

Based on the literature collected, clinical surveillance to this point has been largely focused on process measures, HRQL, health-related PROs and other PRO measures. The reason is likely to be expediency—developing and implementing long-term health outcome measures is challenging and requires short-term resources to achieve longer-term gain in improved health care. In addition, collecting accurate data on health outcomes is just a first step in utilizing the value equation. The second step, collecting episodic (minimally) or longitudinal (ideally) cost data has also been reported to be challenging within the US health care system. However, there appears to be continuing development of processes and instruments to support outcome and cost measurement.

Based on the findings, there were differences in perception of the current status of health outcomes measurement in clinical genetics. In a systematic review of articles on outcome measures in clinical genetic services, Chou et al.<sup>56</sup> found that only three of 55 articles reported on health outcomes. In a systematic review of articles on outcome measures in common chronic diseases with a genetic component, Scheuner et al.<sup>60</sup> found that only four of 16 studies reported a health outcome. Over the course of seven commissioned systematic reviews on genetic/genomic tests and related interventions, the EGAPP Working Group found sufficient evidence to support only one positive recommendation (Lynch syndrome recommendation), with a key link in the evidence chain based on only two observational studies.

However, targeted searches of the literature identified genetic disease-specific primary articles (and one systematic review) on health outcome and other PRO measures. Those presented in the review were selected from more developed outcome frameworks, and may not be representative of other diseases. In several other diseases reviewed, each primary article addressed only one health outcome or HRQL/PRO measure, so comprehensive disease-specific searches would be needed to determine the amount, quality and consistency of health outcome information overall. More review may be needed to understand these observed differences.

The later sections of KQ 4 reviewed experience of existing process and investigators in developing and validating non-genetic quality indicators and outcome measures. While the processes/systems are not likely to be directly applicable to genetic diagnosis, the concepts and some lessons learned should be. Some processes (e.g., American College of Cardiology/American Heart Association and NQMC) may be candidates for collaborative efforts, and several may benefit from input from clinical geneticists. The sections on potential genetic-specific and general barriers to development and implementation of outcomes measurement represent opinions, but relatively informed opinions. Appropriate consideration may avoid



potential pitfalls. Themes from these comments can be found in the Synthesis and Discussion section.

Health outcomes measurement is essential to researchers in order to understand disease progression and the net balance of benefits and harms resulting from interventions (clinical utility).<sup>52</sup> Determining clinical utility is equally essential to health care providers and policy makers in order to establish clinical guidelines that define eligible target populations and other variables that establish appropriate utilization. This information is also important to inform economic analyses, justify reimbursement and support possible introduction of the intervention into public health programs.

It appears to be generally assumed, but less often stated, that health outcomes matter to patients,<sup>17,119</sup> and in many cases are relevant to family members (though patients may or may not choose to share the information). However, establishing a genetic diagnosis that provides information on risks and prognosis (e.g., morbidity, mortality, possible interventions or treatment, function, symptom progression or improvement) will not improve short- and long-term health outcomes in a proportion of genetic diseases for which there is no effective intervention. However, the information associated with the diagnosis may still have value (see KQ5), and other outcome measures may be of more relevance (e.g., early diagnosis, quality of life, access to services and support) to patients and health care providers in such cases.

### **Quality of Findings**

Among the 57 individual general articles/documents addressing KQ4, 26 were graded *Good*, 26 *Fair* and five *Poor*. Among the 14 studies referenced; six were graded *Good*, and eight *Fair*.

The range of findings reported in this section can be generally divided into information on health outcomes and health outcome hierarchies or on the processes used to identify, validate and test or implement health or other outcome measures. The overall knowledge generated was classified as *Adequate*. It is important to acknowledge both the potential generalizability and/or immediate usefulness of some findings, as well as the potential for future real world experience to add to this knowledge base and set standards for these processes.

## FINDINGS FOR KEY QUESTION 5:

***What specific outcomes have been proposed that provide other utility (e.g., personal utility) to the individual, family members, health care delivery systems or public health in general? How does establishing a genetic (or other) diagnosis contribute to improvement in these outcomes?***

*"It is possible for personal genomic information to have no utility for patient's outcomes, but nonetheless to have clinical utility due to informational impacts on clinicians and patients that change the former's decision making or improve the latter's adherence to clinical advice. The question then becomes whether the information is to be funded collectively (societal) or individually..(or)..may justify the expenditure of limited societal resources."<sup>77</sup>*

*"...utility of genomic information (may) be considered from three perspectives: the public health perspective, which emphasizes health improvements on a population level; the clinical perspective, which emphasizes the use of genomic information in diagnostic thinking and therapeutic choice; and the personal perspective, which may consider genomic information as having potential value per se, positive or negative, regardless of its clinical use or health outcomes."<sup>65</sup>*

*"An outcome can be any measure that affects the health, perceived health, physiologic function, financial status, or experience of a patient."<sup>73</sup>*

In large part, the categories of outcomes that have been proposed to provide clinical utility other than direct impact on health (e.g., morbidity, disability, mortality) have already been described as part of the outcomes hierarchies identified in KQ4. These categories include information of immediate clinical importance to clinicians and patients, such as HRQL and patient-reported measures of health outcomes. These categories also include described measures of personal utility<sup>65,77,107</sup> (e.g., value of information, ending a diagnostic odyssey), and of more "humanistic" patient-reported and "patient-centered" outcome measures such as compassion, respect, choice, hope, and opportunity for therapeutic benefit.<sup>81</sup> Some categories include outcomes that relate to the impact of genetic information on patients' family members (e.g., satisfaction, empowerment, value of genetic information or diagnosis). What follows is an overview from the articles and documents identified by the initial searches, including definitions and examples. It is by no means comprehensive, as the literature of primary studies on these topics is very large, and summarization of the primary findings was beyond the scope of this review.

### **Health Related Quality of Life (HRQL)**

*"The concept of quality of life is distinct from health, though related to it."<sup>98</sup>*

*"The addition of patient-focused outcomes allows for the patients and their representatives to provide meaningful measures of quality of life, which may be different than the clinician's perception. A clinician may interpret the improvement of a biochemical marker as a response to therapy, although there is no perceived benefit from the patient."<sup>86</sup>*

The concept of health-related quality of life (HRQL) began in the 1980's, and has evolved to “..encompass those aspects of overall quality of life that can be clearly shown to effect health – either physical or mental” (<http://www.cdc.gov/hrqol/concept.htm>). Laboratory and radiographic or imaging results and clinical assessments of function are objective measures of a disorder or condition. Measurement of HRQL provides subjective information on the impact of a disorder/condition, characterizes what the patient has experienced as the result of medical care, and is an important supplement to traditional measures of health status.<sup>98 73</sup>

Conversion of subjective assessment of HRQL into objective data requires identification of measurable elements that can be assessed using an *instrument*.<sup>73</sup> Concepts that define the scope of such an instrument include: (1) impairment, (2) functional state, (3) health perception, (4) social opportunity, and (5) duration of life. These concepts are translated into domains for which there are measurable data<sup>73,98</sup>:

- physical functioning
- social functioning
- emotional functioning
- cognitive functioning
- pain/discomfort
- vitality (*e.g.*, energy, fatigue)
- overall well-being.

Clinical results, such as “measures of biological and physiological function, tissue diagnoses, and patient-reported symptoms, are only occasionally included in conceptualizations of HRQL”.<sup>98</sup>

Reliable and validated HRQL outcome measures are available for the general population, but may not apply to age, gender or disease-specific groups, particularly those with specific genetic disorders characterized by significant cognitive and/or physical impairment.<sup>74,86</sup> Combined measures of health status and HRQL are commonly used in some other specialties. McAllister et al.<sup>133</sup> noted that, while measures of health outcomes may not be as applicable to genetic diagnoses for which treatment is not available, HRQL measures have value to both patients and health care providers.<sup>13,48,86</sup> HRQL is generally measured using patient-reported outcome instruments, usually short self-completed questionnaires. Validated generic measures of HRQL are available, and one specific for clinical genetics is in validation.<sup>133</sup> An advantage of HRQL instruments may be that they omit domains of health found in more clinically oriented instruments, and focus on issues important to patients.<sup>52</sup> However, HRQL instruments might also omit important domains of health that may predict important future clinical outcomes.<sup>52</sup> The findings did not allow an estimate of the total number of validated disease-specific or outcome-specific instruments for measuring HRQL that are available and applicable in clinical genetics.

One example related to neurofibromatosis type 1 (NF1) was reported by Stevenson et al.<sup>86</sup> in 2009. The impact of NF1 on quality of life had been previously reported using several HRQL

measures, but the authors were concerned that HRQL tools effective for one manifestation of NF1 such as attention-deficit/hyperactivity disorder might not be appropriate to assess HRQL for tibial pseudarthrosis. Health outcomes related to tibial dysplasia and pseudarthrosis are serious, and include the number of surgeries necessary to achieve bony union of a fracture, decreased range of motion, pain, limitation of walking distance, gait disturbance, and amputation. To assess HRQL outcomes, the authors selected the Pediatric Outcome Data Collection Instrument (PODCI) developed in 1998<sup>153</sup> and validated in orthopedics in 2001<sup>154</sup>. To assess HRQL outcomes, the authors selected the Pediatric Outcome Data Collection Instrument (PODCI) developed in 1998<sup>153</sup> and validated in orthopedics in 2001<sup>154</sup>. This instrument used 117 questions in five domains:

- Global functioning
- Extremity and physical function
- Transfers and basic mobility
- Sport/physical function
- Pain/comfort
- Happiness

They showed that the PODCI could detect differences in perceived HRQL between patients with NF1 and tibial dysplasia versus control patients with NF1 only.

### **Patient-Reported Outcomes (PRO)**

PRO is an umbrella term that potentially includes a wide range of subjective measurement types, but specifically refers to self-reports by the patient. Information may be collected using questionnaires completed by the patient or through interview.<sup>87</sup> However, to qualify as a PRO, the interviewer must faithfully document the patient's views, not make a professional judgment on the impact of the information on the patient's health status. Since PROs include HRQL, there was some confusion about definitions and instruments. In an attempt at clarification, the FDA released a guidance document for industry in 2009.<sup>155</sup> The FDA defined a PRO, based on the source of the information rather than the content, as:

*"...a measurement of any aspect of a patient's health status that comes directly from the patient (i.e., without the interpretation of the patient's responses by a physician or anyone else)"<sup>155</sup>*

HRQL is among the most important of the outcomes encompassed by this definition.

In 2008, Valderas proposed a classification system for PROs based on three concepts:<sup>87</sup>

- The construct is defined as the measurement object, or the range of characteristics measured by the survey instrument (e.g., symptoms, functional status, health perceptions, HRQL, material well-being, satisfaction with care, productivity, intimacy, safety, and community and emotional well-being and care compliance<sup>78</sup>).
- The population is the "universe of persons" for which the survey instrument is appropriate.

The measurement model includes the *metric* or method used to assign values/scores (e.g., psychometric, clinimetric, econometric), the *dimensionality* or number of scores per Table 8.

**Table 8. Application of the Valderas classification system to two PRO instruments**  
(modified from Table 3 in Valderas et al.<sup>87</sup>)

	<b>Construct</b>	<b>Population</b>	<b>Measurement</b>
MOS SF-36 <sup>a</sup>	Symptoms Functional status Health perceptions	Adults All genders All diseases	Profile Psychometric Completely standardized
<b>KIDSCREEN<sup>b</sup></b>	Functional status Health perceptions Quality of life	Children & Adolescents All genders All diseases	Profile Psychometric Completely standardized

<sup>a</sup> Multi-purpose, short-form health survey with 36 questions; profile of functional health and well-being score; psychometric physical and mental health measures; preference-based health utility index.

<sup>b</sup> Multiple instruments; long version covers 10 HRQL dimensions, short version covers 5; KIDSCREEN Index provides global HRQL score.

- individual (e.g., index, profile) and the adaptability or the extent the instrument can be tailored to circumstances (e.g., completely or partially standardized, individualized).

Application of this system to 15 frequently used instruments (e.g., MOS SF-36, EuroQol, Kidscreen, EORTC QLQ-C30) demonstrated feasibility of use, and showed that most instruments assess more than one construct. Results from two instruments are provided in Table 8.

The FDA provided a detailed list of characteristics of a PRO instrument<sup>155</sup>

- Number of *items or measures*
- Conceptual framework of the instrument
- Characteristics of disease/condition and treatment for intended use
- Population for intended use
- Data collection method and quality control
- Administration mode
- Format and response options (e.g., Likert scale, checklist)
- Patient recall period (e.g., depends on purpose and intended use)
- Scoring method
- Weighting of *items/measures or domains*
- Respondent burden
- Reliability (e.g., content and construct validity)
- Availability of translation or cultural adaptation

The FDA also identified the key characteristics that can affect success of an instrument:

- Clarity or relevance
- Response range
- Variability
- Reproducibility
- Inter-item correlation
- Ability to detect change
- Discrimination
- Redundancy
- Recall period

In 2010, Cella et al.<sup>52</sup> reported results from the first large-scale testing of *items (measures)* from the Patient-Reported Outcomes Measurement Information System (PROMIS). Based on their belief that currently available PRO measures have been “limited by a lack of precision, standardization, and comparability of scores across studies and diseases”, the PROMIS project aims to assemble “item banks” (*i.e.*, lexicons, lists) of HRQL and PRO measures that can be used for developing HRQL / PRO instruments, some using computerized adaptive testing.<sup>52</sup> The PROMIS web site (<http://www.nihpromis.org/>) states that their goal is to “..build and validate instruments that measure feelings, functions and perceptions applicable to a range of conditions for ..clinical practice application” of PROs. For the study, short forms from each bank were developed and compared with other well-validated and widely accepted (“legacy”) measures. The authors conclude that PROMIS items and short forms provide evidence of reliability and validity.<sup>52</sup> Further testing is planned in diverse clinical populations. It is not clear whether these measures will have better applicability to clinical genetics than other validated instruments. More information on PROMIS can be found in Figure B4 (Appendix B).

### **Patient satisfaction**

*“Patient satisfaction with healthcare may be conceptualized as a comparison between what is expected and what is received.”<sup>53</sup>*

Where does patient satisfaction fit in? It is variably referred to as a process measure<sup>5</sup> and a PRO<sup>87</sup>. The answer may lie in the fact that patient satisfaction has multiple meanings in value measurement. Patient satisfaction with care (*e.g.*, amenities, friendliness, convenience, service experience) is generally considered a process measure. However, patient satisfaction can also be a measure for compliance and health outcomes as perceived by the patient (*e.g.*, functional status, pain, anxiety, and other factors for which objective markers are not available).<sup>87</sup> Functionally, patient satisfaction with healthcare is often measured through self-report using quantitative and qualitative methods or as part of a PRO instrument. Measurement of patient satisfaction may be variable over time and for different health care encounters.<sup>53,84</sup> At least satisfaction surveys have been validated for use in clinical genetics settings and one is in validation<sup>53,55,104,156</sup>.

Instrument	Domains/constructs Assessed
Satisfaction with Genetic Counseling Scale (SGCS) <sup>53</sup> (12 item) Satisfaction	Instrumental, affective, procedural satisfaction, satisfaction with information, fulfillment of expectations, and overall satisfaction.
Genetic Counseling Satisfaction Scale (GCSS) <sup>53</sup> (6 item)	Satisfaction with perceived counselor understanding, knowledge, reassurance, concern, session length, and overall value of session.
Patient Satisfaction Questionnaire for the Clinical Genetics Setting <sup>55</sup> (7 question)	Patient questions answered, respect given, time spent, and responsiveness.
Genetic Counseling Outcome Scale (GCOS-24) <sup>156</sup> (24 question) – in validation (Table B18, App. B)	Patient-reported outcome measures, such as HRQL, PPC, anxiety, depression, health locus of control and empowerment.

## Empowerment

*Empowerment* is an aspect of HRQL, and is described as: “a set of beliefs that enable a person from a family affected by a genetic condition to feel that they have some control over and hope for the future.”<sup>43</sup> The four dimensions include:

- *Decision making (Decisional control)*: can make important life decisions in an informed way;
- *Knowledge and understanding (Cognitive control)*: has sufficient information about the condition, including risks to oneself and one’s relatives, and any treatment, prevention and support available;
- *Instrumentality (Behavioral control)*: can find and make effective use of the health and social care systems for the benefit of the whole family;
- *Future orientation (hope)*: can look to the future having hope for a fulfilling family life, for oneself, one’s family and/or one’s future descendants (e.g., know about ongoing research, finding support to give greater confidence and hope)."

Empowerment has some similarities to constructs captured by the Multidimensional Health Locus of Control (MHLC) scales. However, the MHLC is focused on health of the individual, while empowerment includes how genetic conditions have broader impacts on health decisions in families. Empowerment is also similar to the concept of perceived personal control (PPC), the existing outcome measure observed in the study that most closely captures patient beliefs about clinical genetics. However, the authors believe that PPC lacks future orientation (e.g., risks and threat to future generations, responsibility).<sup>43</sup>

## Diagnostic/prognostic uncertainty

*"Diagnostic and prognostic uncertainty is one of the major psychological stressors for patients in acute and chronic illness, as well as for parents of children with disabilities or chronic disease."*<sup>40</sup>

This is particularly true in genetics clinics when encountering a child with symptoms or anomalies suggesting an underlying syndrome, but for whom a definitive diagnosis has not been found. Due to the complex, rare and multi-system nature of genetic conditions, patients may experience a stressful, onerous and expensive “diagnostic odyssey” before obtaining a definitive diagnosis.<sup>45,48</sup> Primary care physicians may refer for separate treatment of multiple symptoms. Even if the unifying cause is recognized and a diagnosis made, patients may remain under the care of several specialists with little coordination of care. Even in the absence of effective intervention, prognostic information about the disorder may enable life planning.<sup>80</sup> Table 9 summarizes the results of seven qualitative studies investigating the impact of diagnostic uncertainty. While an effect was not seen in two studies, the results suggest that some families of children do benefit from obtaining an early and direct diagnosis for their child’s problems.<sup>39,40,42,48,50,51,121</sup> However, it is not clear whether the effect relates to receiving a specific diagnosis or professional confirmation of a serious disability that requires special services, or whether the parents’ ability to adapt to and cope is related to knowing a specific genetic cause.<sup>42</sup>

### **Personal utility**

*“Calibrating measures of personal utility..may be more problematic..What degree of negative psychological affect from risk estimation, for example, outweighs positive changes in screening or lifestyle behaviors?”*

As noted in section KQ 4a, clinical utility in its broadest sense “..can refer to any outcomes considered important to individuals and families”<sup>64</sup>, hence the term *personal utility*.<sup>65,77,107</sup> Personal utility is the term most commonly used when talking about patient-reported or “patient-related/patient-centered” outcomes and outcome measures in the context of clinical genetics. Important examples include:

- Positive effect of genetic information on a person’s life even if direct health benefits are small or non-existent.
- Value of information even if there is no personal intent to use the information to guide management or prevention strategies.<sup>65</sup>
- Value received from a genetic diagnosis even when the diagnosis does not change medical management or when treatment is not available
- An end to the “diagnostic odyssey”

Some of the outcomes and outcome measures discussed in sections above have also been cited as measures of personal utility. There is certainly an ongoing need to develop specific metrics/measures for personal utility in clinical genetics, and to articulate exactly what outcomes are feasible to measure. Another approach would be to review existing measures from other known instruments and from PROMIS and other measure developers to see if applicable measures exist or can be adapted.<sup>52</sup>



Foster et al.<sup>77</sup> propose that personal utility measures should be combined with measures of clinical utility, including patient health outcomes, impact of information on physicians, and impact of information on patients (adherence), in order to compute aggregate estimates of benefits. Foster also questions whether cost in the value equation should be individual or societal or both. These are interesting concepts, but, as Grosse et al. point out, “..they do not provide practical advice on how to do so.”<sup>65</sup>

**Table 9. Qualitative studies investigating the impact of diagnostic uncertainty and the potential value of a genetic diagnosis.**

Study	Site(s)	Subjects	Method	N	Diagnosis impact themes	Value of diagnosis
Rosenthal, 2001 <sup>50</sup>	NIH/NHGRI; Vermont, University of Wisconsin	Parents of children w/ unexplained MCAs	Qualitative study: Individual phone interviews, audiotaped; open-ended questions w/ follow-up	29 parents of 16 children	Labels Cause/etiology Prognosis Treatment Acceptance Social support	Wide range of interest in diagnosis More motivated when child younger Some ambivalent Wanted if offered
Lenhard, 2005 <sup>40</sup>	Germany	Mothers of children with Down syndrome, MR of unknown origin and non-disabled controls	Questionnaires sent home with children at special/ elementary schools  STAI – trait anxiety index Emotional burden; feelings of regret	411 Down syndrome 66 MR unk, 69 non-disabled	Psycho-emotional disadvantages for mothers of children w/ MR unk origin ( $p < 0.01$ ); less likely to join support group Mothers of DS and non-disabled scores similar	Less emotional strain and regret
Geelhoed, 2008 <sup>121</sup>	Western Australia	Parents of children <16 yrs w/ nonsyndromal congenital deafness	Retrospective group selected by medical genetics record review & identifying families of children tested Prospective families invited at first consultation Offered dx tests, clinical & family hx, questionnaires	14 retrospective 35 prospective	Better understanding of child's condition Encouraged discussion Useful for family planning Relief at finding a cause	96% perceived benefit from testing
Graungaard, 2009 <sup>39</sup>	Denmark	Parents of single severe mentally/ physically disabled child recruited from neuro-pediatric/ neonatal wards & Clinical genetics; 1-2 yrs of age	Qualitative longitudinal interview study Semi-structured in-depth interviews with each parent, audiotaped	16 parents	Creating future images Identifying possibilities for actions Perceiving the child Communicating with health professionals Implicit expectations of healthcare system	Parents experiences and coping possibilities strongly influenced by the diagnostic process and the certainty of the stated diagnosis

<b>Study</b>	<b>Site(s)</b>	<b>Subjects</b>	<b>Method</b>	<b>N</b>	<b>Diagnosis impact themes</b>	<b>Value of diagnosis</b>
Makela, 2009 <sup>42</sup>	British Columbia, Canada	English speaking parents of a child 5-10 yrs of age with intellectual disability (ID)	Demographic information, semi-structured open-ended interviews, chart reviews to confirm diagnosis	10 w/ diagnosis, 10 idiopathic	Validation Information to guide expectations & Tx Services in school system/community Support Need to know-curiosity Prenatal testing	No differences in parents' perceptions or experiences related to presence or absence of etiological diagnosis for ID
Lewis, 2010 <sup>41</sup>	United Kingdom	Parents of a children of varying age seen at the genetic clinic with only working diagnosis or no diagnosis	Qualitative grounded theory method Semi-structured interviews on feelings about getting diagnosis	14 parents	Help with care & Tx Emotional impact Coping mechanisms	Some experiences common to parents with diagnosed child Lack of diagnosis "adds a layer of complexity"
Statham, 2010 <sup>51</sup>	United Kingdom/Ireland	Family members with many boys or men with ID of unknown etiology, many involved in the Genetics of Learning Disability (GOLD) Study	Qualitative - Interviews in participants' homes w/ transcription	120 members of 37 kinships	Provide benefits & explanation Use for reproductive choice Help provide education/other services	Diagnosis wanted to enable other family members to have reproductive choices

In summary for KQ5, categories of outcomes that provide “other utility” to individual patients and family members have been described, along with some characteristics of the instruments used to measure the outcomes. Health status PROs and HRQL are “health outcomes” from a patient perspective. While these outcome measures are important in clinical management and fit equally well in KQ4 and KQ5, we elected to describe them as part of KQ5. Table 7 in KQ4 illustrates a level of consistency in outcome measures between outcome hierarchies in the categories of PROs/HRQL and Other PROs. However, it does not capture the large number of concepts (Tables B7, B8, B11, Appendix B) and the extensive clinical research that underlie the range of personal utility and “patient-centered” outcomes.

Based on the findings, it seems that establishing a genetic diagnosis could have negative as well as positive impacts on patients and their families related to a number of these outcomes. The studies on diagnostic/ prognostic uncertainty illustrate a situation in which a genetic diagnosis can have value to the patient and the patient’s family members by providing a definitive diagnosis, information about prognosis and risks, access to medical, educational and personal support, and, perhaps, empowerment. Conversely, establishing a genetic diagnosis could lead to difficult decisions and psychological impact such as worry, stress and difficulty coping. Ideally, use of relevant outcome measures could identify negative impacts and provide the support needed to mitigate the problems identified.

Health plans and payers most often focus on justifying services by documenting improvement in health outcomes. The findings did not address the extent to which patient-reported health outcomes (e.g., functional status), HRQL and other PROs are considered along with morbidity and mortality data by health plans and payers. While the public health perspective generally focuses on evidence-based health improvements at a population level, there has been support from the public health perspective for consideration of the value of personal utility even in the absence of impact on health outcomes.<sup>64,65,95</sup>

## **Quality of Findings**

Among the 16 individual general articles/documents addressing KQ5, nine were graded *Good*, six *Fair* and one *Poor*. Three of the seven studies in Table 9 were graded *Good*, and four *Fair*. Among the eight other studies referenced; one was graded *Good*, six *Fair* and one *Poor*.

The overall knowledge generated was classified as *Adequate*, and in this case represented both concepts along with descriptive and practical information. The focus of the findings was the patient and family perspective, encompassing personal utility, HRQL and other patient-reported outcomes, and other issues of importance to patients and families (e.g., patient satisfaction, empowerment, impact of diagnostic and prognostic uncertainty). A noted *Convincing* characteristic included provision of information relevant to possible directions for change in current practice. However, the information identified lacked diversity in perspectives on the concepts presented.

## **KEY QUESTION 6 – NOT ADDRESSED AS DESCRIBED IN METHODS**

***What approaches have been used to measure the economic impact of establishing a genetic (or other) diagnosis? Each question on economic analyses will be addressed from multiple perspectives: patients, family members, health care providers, payers, health care sector, and society.***

- a. Describe the variables that will be considered in determining costs (e.g., costs to the patient versus the health care system and/or society; costs for a single encounter or “episode of care” versus multi-specialty and/or long-term care).***
- b. What economic models might be / have been used as part of economic analyses of genetic diagnoses or clinical genetic services?***
- c. What metrics might be / have been used to measure the economic impact of genetic diagnoses or clinical genetic services (e.g., QALYs, willingness to pay, direct costs***

Documenting the value of establishing a genetic diagnosis in a specific clinical scenario requires two components: defining and collecting information on outcome(s) of interest and collecting the relevant information on the associated costs. Early in the review process, it became clear that the review would need to focus on the numerator of the value equation, outcomes, with collection and analysis of data on costs and economic models deferred. As previously described, Key Question 6 was removed from the scope of this review.

## SYNTHESIS AND DISCUSSION OF FINDINGS

### Outcomes Hierarchies

Setting aside the category terminology associated with outcomes of health care interventions (e.g., clinical utility, health outcomes, HRQL outcomes, PROs, personal utility or “patient-centered” outcomes), all of these outcomes are important to patients. The level of importance of specific outcomes may certainly vary depending on the patient’s (or family members’) circumstances, experience, culture and other variables. The findings suggest that this categorization of outcomes developed over time in response to:

- a growing understanding of the importance of patient and family member perspective on outcomes of clinical interventions;
- the development, validation and implementation of new instruments that measured specific types of outcomes; and
- the emerging argument for “softening” the focus on core health outcomes (e.g., morbidity, mortality) as the sole deciding factor in reimbursement and/or implementation decisions.

However, the categories clearly overlap, and these outcomes could reasonably be represented as a continuum.

For application to genetic diagnoses, the findings suggest that outcomes related to both clinical and personal utility must be considered. Outcomes related to personal utility may provide important information in addition to health outcomes/clinical utility in patients with genetic disorders for which there are treatments or other interventions, and may provide primary outcome measures of interest to providers, patients and families when medical interventions are limited or lacking.

Questions for consideration:

- What can be learned from the outcome hierarchies and models identified? What components might be applied to building an outcomes framework that will be effective for genetic diagnoses?
- What about the genetic-disease specific outcomes studies in the literature? What is the role of this information and how can it be most effectively collected and summarized?

These questions may be addressed differently based on how the Committee may want to use the information gleaned from these two sources. For example:

- Outcome selection for study protocols  
Bryant et al.<sup>38</sup> proposed that the selection of measures of health for studies of interventions should: “..align itself with the objectives of the study,..reflect a comprehensive understanding of the disease or injury of interest,..the expected benefits and harms of the proposed intervention..and how benefits and harms will affect the patient’s ability to perform day-to-day activities, participate in social activities, and fulfill

societal expectations.” The validity of any measurement instruments must also be demonstrated before used to measure outcomes. It seems this advice, though developed for orthopedic outcomes studies, would also have application to genetic diagnoses.

Since primary studies will generally be disease-specific, review of the literature would be integral to study planning, and should identify available information on health and other outcomes previously studied and the measures that were used. In the absence of such results, outcome hierarchies and existing methods for outcome measure development may be helpful, but possible limitations (*e.g.*, not disease- or context-specific) should be considered. For example, the longitudinal nature of the Porter health outcomes hierarchy prompts consideration of a range of short- and long-term outcomes in different domains (*e.g.*, recovery process, health status achieved, sustainability of health), and Valderas focuses on HRQL and other PRO measures.

- Evaluation of clinical utility to support policy and/or reimbursement decisions

Such evaluation has most often been initiated by performing a systematic review of the published and grey literature on clinical utility (and usually clinical validity), ideally from high quality clinical studies. The data on the observed benefits and harms of the intervention were then analyzed, and the quality of individual studies and overall strength of the evidence was assessed. If the evidence was of sufficient quantity and quality, these data have formed the basis of such decision-making. The significance of the outcome hierarchies in this context could be to remind review planners to consider clearly defined health outcomes, as well as outcome measures related to “broader” interpretations of clinical utility (*e.g.*, PROs, avoidance of diagnostic odyssey, personal utility), and to determine whether they should be investigated as part of a review of a particular clinical intervention.

- Collection of health (or relevant process and/or structure) outcomes in clinical practice as part of a quality improvement (QI) system

The findings included no argument with the concept that reliable information on informative health outcome measures is necessary to understand and improve quality and value in health care. However, it needs to be determined what combination of outcomes and outcome measures have been and/or will be relevant in different clinical contexts. The challenges associated with “real world” collection of accurate and reliable outcomes data have been discussed.

The benefits of real world data include: collection of data from diverse practice settings and patient populations; deriving estimates of effectiveness rather than efficacy (*e.g.*, value of an intervention in clinical practice versus in controlled conditions such as a study); the potential for looking at a broader range of outcomes than a study could support; and addressing diseases for which studies are not feasible (*e.g.*, rare disorders, a pressing need for an answer). The limitations of real world data collection are that the process may: require significant resources; involve linkage of clinical data to claims data

(or other sources of data); have potential for bias; and raise questions about confidentiality and appropriate storage and handling of patient data.

A related challenge is to ensure that the specific pieces of data collected to measure outcomes will be consistent and comparable across geographic locations and different health care settings. It would also appear that the selection process for such measures should begin with published (and possibly grey) literature review in order to capture any existing information related to an outcome measure of interest. Such information may come from clinical studies or systematic reviews, illustrating the closely interrelated nature of these processes.

### **Challenges and barriers to collecting outcomes of interest**

As the sections in KQ4 on barriers from clinical genetics and general perspectives describe, there are some key conceptual questions to be addressed (some modified from Brooten<sup>72</sup>):

- What outcomes matter and to whom – patients and family, health care providers, health care payers and purchasers, and society?
- Who is willing to pay the costs for developing processes and measures, measuring outcomes and documenting improvements, or translating results into improved outcomes?
- How to determine the magnitude of the intervention needed to produce a change in outcome?

More general questions include:

- How to identify methods that will ensure the validity and reliability of measures?
- How to develop approaches that lessen the burden of collecting data?
- How to deal with in the short-term, and remedy in the long term, the lack of defined and validated outcome measures?
  - Disease-specific measurement scales often lacking
  - Generic measures may be insufficiently sensitive or expensive

For a proportion of genetic disorders, clinical geneticists cannot provide health benefits in the traditional sense (*i.e.*, effective treatment or cure). There needs to be consideration of other options, and to what extent these options are applicable to specific clinical situations. For example, measuring the degree to which other interventions (*e.g.*, diagnosis, risk, prognostic information, services/support) and measures of informed decision-making or psychosocial effects can provide benefit to patients and families.

Other identified barriers to be addressed related to genetic diagnoses and clinical genetic services:

- Difficulty obtaining data on rare diseases, complicated by potential coding overlaps
- Treatment may involve multiple interventions and multiple specialty providers



- Relatively small number of clinical genetics professionals
- Rapid change, with new treatments emerging for previously “untreatable” disorders
- Clinical genetic outcome measures/indicators rarely included in electronic medical records (EMRs)
- Shift in emphasis needed from more available outcome information to effectiveness of care and impact on short- and long-term health outcomes

More generic issues include:

- Requirement for resources and expertise to review literature, develop and validate data collection tools/instruments and analyze results
- Capturing functional status and other outcomes that are buried in patient charts and free text fields in EMRs
- Costs of collecting longitudinal outcomes high due to current fragmented health care system and lack of interlinked EMR
- Difficulty of establishing causal links between tests or interventions and changes in mortality, morbidity, quality of life, function and other core health outcomes

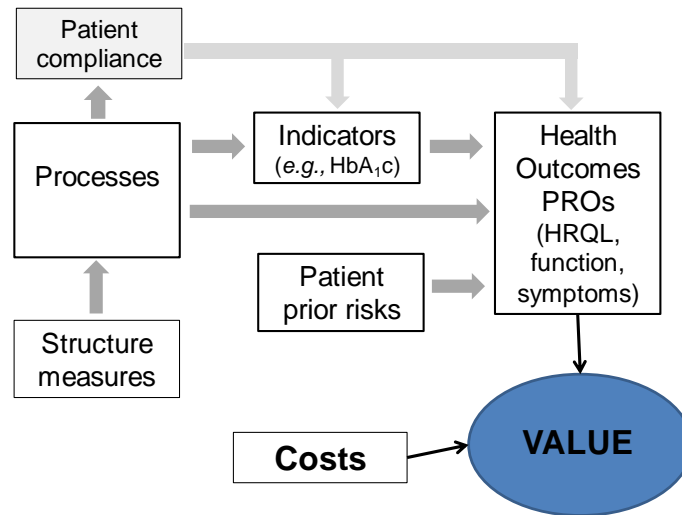
#### Moving Toward a Value Model for Genetic Diagnoses

*“..assessing needs and outcomes cannot be merely seen as a technical exercise..but contextualized by a value framework whereby the making of choices becomes explicit.”<sup>103</sup>*

The models identified in KQ2 range from the very simple (Donabedian) to very complex (Valderas). Donabedian touched on, and Porter described in detail, the relationship between outcomes / quality and costs in determining value, though even Porter did not include cost in his model. As noted previously, the usefulness of such models to different stakeholders – in this case clinical genetics professionals / ACMG – is not known. However, it seems that the ability to formulate a model may be helpful in clearly articulating the key theoretical components of a proposed process for determining value. As an example, Figure 10 illustrates how the Porter model (Figure 5) could be rearranged to minimize structure measures and direct application of process measures, maintain the focus on health outcomes, and add cost as a key variable. Note that this model is not intended as a suggested approach, but rather simply an example of modifying a model to suit (and characterize) a defined purpose. As always, the “devil is in the detail”. For example a value model for genetic diagnoses might be characterized by:

- choice of outcome types, whether generic or specific to the disorder;
  - health, process, structure outcomes
  - short- and long-term
  - intermediate or surrogate
- choice of specific outcomes that provide information that are measureable and clinically meaningful (*i.e.*, medical management, positive lifestyle choices );
- consideration of other factors that may impact outcomes (*e.g.*, patient prior risk);

- possible assignment of weights to selected outcomes relative to each other and other factors;
- determining if cost data are available for high priority outcomes;
- defining a process for validating, or adopting existing validation of, selected outcome measures; and
- ultimately, determining how cost data or economic analysis will be used to determine value and what metric or metrics will be used.



**Figure 10. A sample model for characterizing the measurement of value in health care**

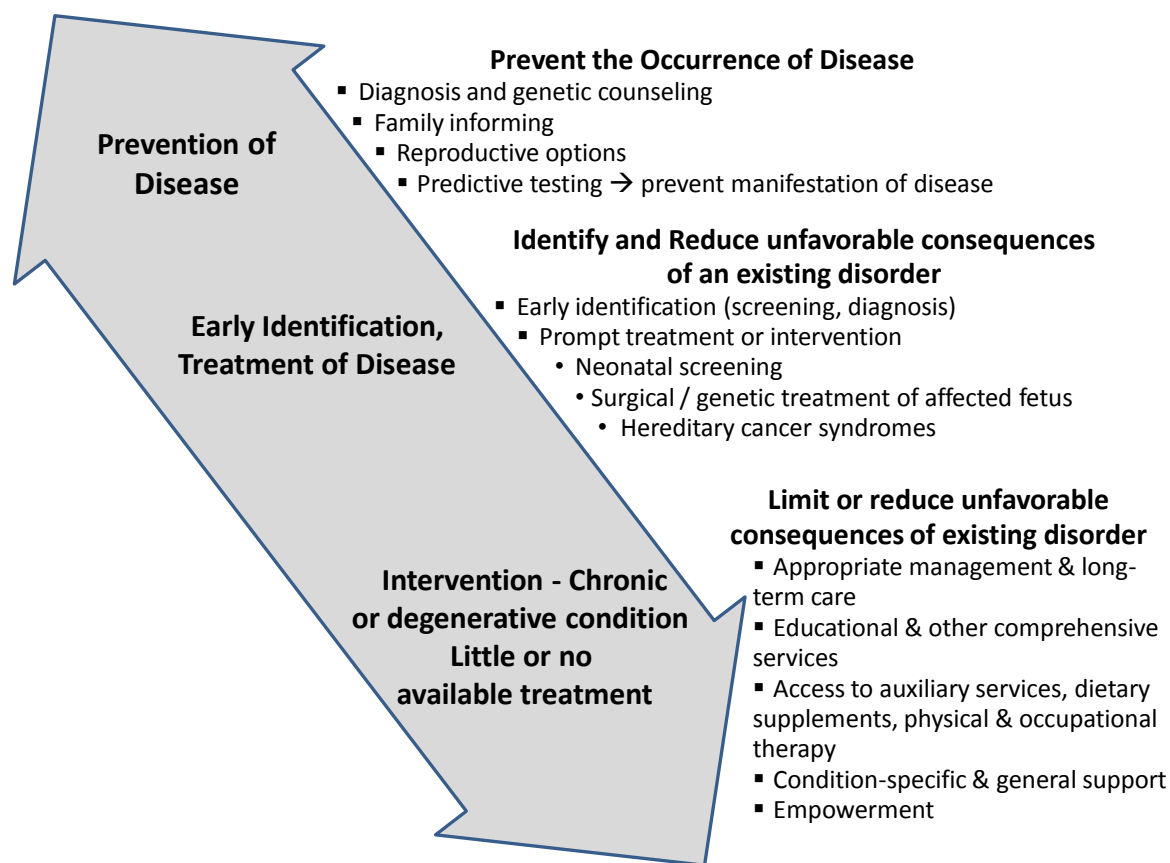
### Outcomes Hierarchy(ies) for Genetic Diagnoses?

*“Ultimately, the goals of genetic services should emphasize long-term health status and improvements in public health. To help frame the broader public health implications of genetic advances, it may be useful to examine health outcomes in terms of primary or secondary prevention of disease, or tertiary intervention of disease complications and suffering.”<sup>84</sup>*

There are, of course, many ways that outcome hierarchies and catalogues of outcome measures could be integrated into a value framework for genetic diagnoses. The concept of considering health outcomes in genetic diagnoses / clinical genetics services in the classic public health context of *primary*, *secondary* and *tertiary* levels of disease prevention was raised by three authors<sup>84,89,126</sup>, and considered to be a useful context with some modification to reflect application in a more clinical context and to acknowledge ongoing changes in clinical genetics

practice. A key advantage of this approach presented in Figure 11 is that it accounts for the subset of genetic diseases for which long-term health outcomes have less or no relevance.

It is important to note that the dividing lines between these three categories are not completely clear. In addition, genetic diseases have begun to move from the lower to the middle category as more is learned about causal pathways and new therapeutics are developed. The three categories might more accurately be viewed as a continuum, but may be useful for purposes of determining the mix of specific outcomes of interest to be addressed and appropriate measures for those outcomes. These categories, or domains of a continuum, would, of course, require more deliberation and definition. Additional consideration would also need to be given to the types of outcomes (e.g., clinical and/or personal utility) that apply to the categories or domains, and to specific disorders that fall within them.



**Figure 11. Considering a continuum of outcomes in the context of potential for clinical intervention**

In addition to the potential for intervention, another important dimension in considering outcomes is perspective. What would be the outcomes of interest at different points in this intervention continuum from the perspective of the many stakeholders within the health care sector, including genetics professionals/clinicians, patients/consumers, health care systems and payers, public health and society? Figures 12A and 12B provide a representation of three outcome dimensions. The x-axis represents the range of outcome measures as presented in Table 7 and Figure 9, and the y-axis represents the range of potential for clinical intervention as presented in Figure 11. Varying perspectives can be illustrated within this two dimensional space.

Figure 12A shows the overarching structure, and assumes the genetic diagnosis is for Lynch syndrome and its impact on family members. Two out of the many potential perspectives are shown as areas within the two dimensional space. Given the preventable nature of Lynch syndrome, the Payer Perspective is more likely to focus on the hard health outcomes in determining value. However, the Patient Perspective is more likely to also include reductions in disease consequences as well as a wider range of outcomes, including HRQL and other PROs. When considering a value framework that would be appropriate for Lynch syndrome, it may be reasonable to include more than just health outcomes.

Figure 12B shows the same overarching structure, but this time the diagnosis is for Tay Sachs disease in a young child. In this example, two different perspectives are shown. To the Health Provider, value is likely to be mainly derived from the HRQL outcome measurements relating to overall well-being and comfort of the child. In contrast, the Public Health Perspective might be more focused on the prevention of the disorder, either by carrier testing of parents and primary prevention, or research into effective treatments or cures.

These examples should not be viewed as being correct or incorrect, rather as simply ways in which a structured approach could be taken in determining whether a proposed value framework might meet the wide-range of clinical scenarios and outcome dimensions that need to be considered.

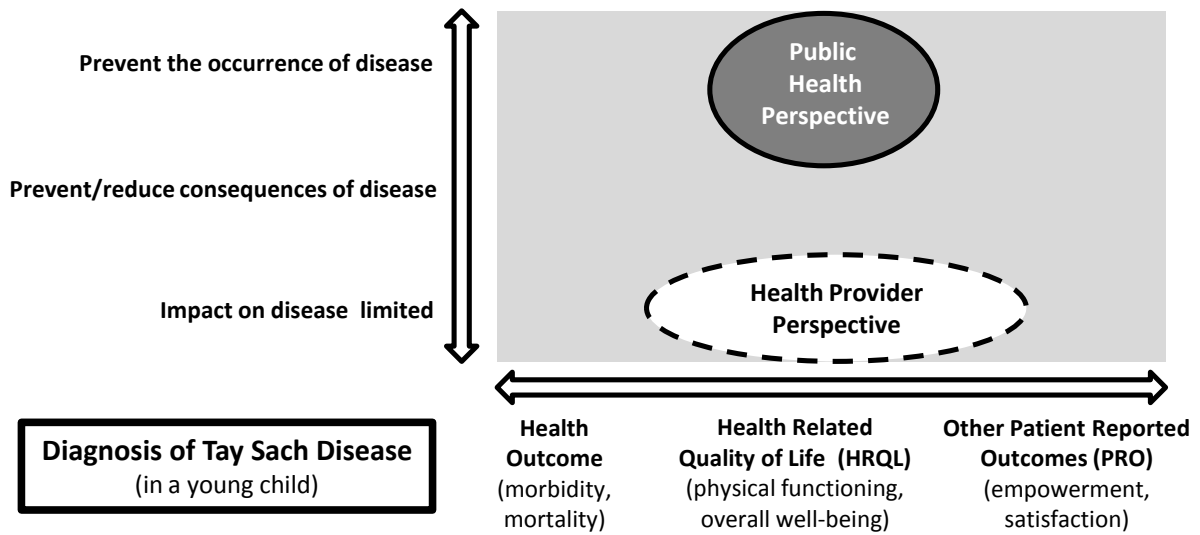


Figure 12 A

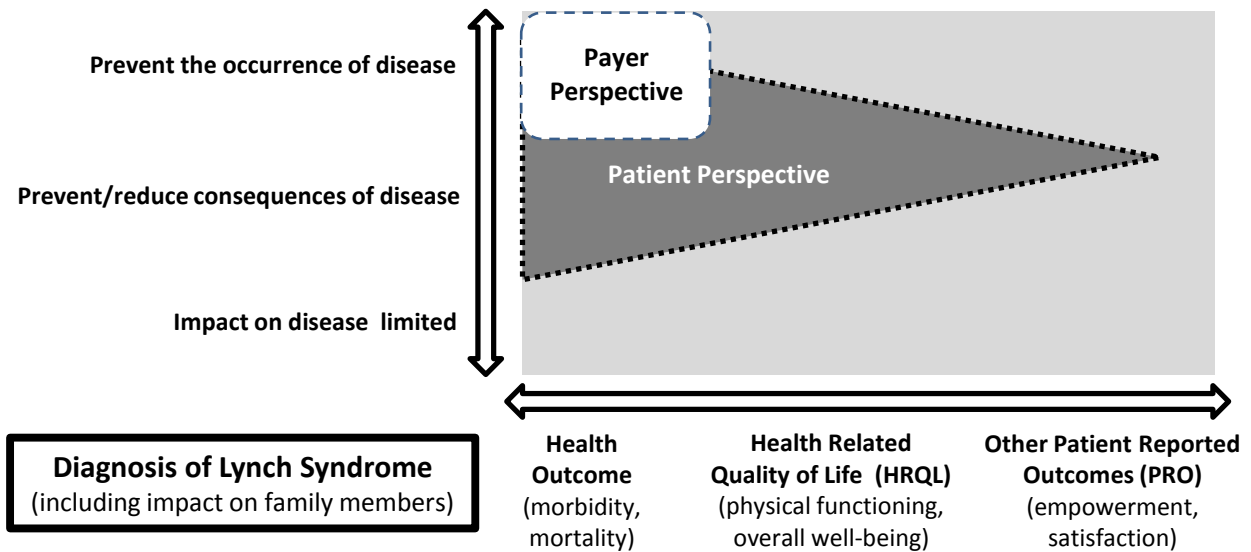


Figure 12 B

**Figures 12A and 12B. Overarching structures for consideration of outcomes** The x-axis represents the range of outcome measures as presented in Table 7 and Figure 9, and the y-axis represents the range of potential for clinical intervention as presented in Figure 11. Varying perspectives can be illustrated within this two dimensional space.

In summary, this qualitative review suggests that no single outcomes framework or hierarchy identified in the published and grey literature is sufficiently comprehensive to represent the range of outcomes and perspectives that may be needed to address the broad range of clinical scenarios related to genetic diagnosis.

However, a rapidly growing knowledge base is available to support the development of a process for informed selection and validation of outcome measures for genetic diagnoses and/or collaboration with existing processes to highlight outcomes of genetic diagnoses that are relevant to or included in other specialty or generic health care outcome lexicons or hierarchies.

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## GLOSSARY OF RELEVANT DEFINITIONS

**Attribute of value:** A component of value (e.g., outcomes, cost).<sup>1</sup>

**Clinical performance:** “The degree of accomplishment of desired health objectives by a clinician or health care organization.”<sup>2</sup>

**Clinical performance measure:** “A subtype of measure that is a mechanism for assessing the degree to which a provider competently and safely delivers clinical services that are appropriate for the patient in the optimal time period.”<sup>2</sup>

**Clinical utility:** Association of a test or intervention with improved clinical outcomes and/or patient and clinician decision-making; encompasses effectiveness (utility in real clinical settings) or efficacy (utility in controlled settings such as clinical trials) and the net balance of risks and benefits associated with using a test in clinical practice; generally specific to the clinical scenario and target population.<sup>3-5</sup> Clinical utility encompasses effectiveness, and the net benefit (the balance of benefits and harms).<sup>5</sup>

**Functional outcomes:** Functional ability that is meaningful to the patient in the context of everyday living.<sup>6</sup>

**Functional status:** A measure of an individual’s ability to perform normal activities of life, including physical functioning, emotional well-being and social functioning.<sup>1</sup>

**Health care sector:** A broadly inclusive term that covers:

- providers of health care from medicine, nursing, pharmacy, allied health, hospital management, health maintenance organizations, biotechnology and medical products developers;
- in primary, secondary and tertiary care settings and public health;
- who are involved in the diagnosis, treatment, and prevention of disease, illness, injury, and other physical and mental impairments in humans.

**Health-related quality of life (HRQL):** The aspects of quality of life that relate specifically to a person’s health, such as function or general health perceptions.<sup>7</sup>

**Objective health measures:** Measure an outcome and, by definition, do not consider the patient’s perspective.<sup>8</sup>

**Outcome:** 1) A change in a patient’s health status (e.g., survival, restoration of function) as a consequence of health care provided.<sup>9</sup> 2) Any measured consequence or impact for the patient of using genetics services.<sup>8</sup>

**Patient-Reported Outcome (PRO):** Report directly from patients about a health condition and its treatment, including symptoms, functional status, HRQL, treatment satisfaction, preference, and adherence.<sup>10</sup>

**Process:** A dimension of quality that includes patient-provider interactions at all levels, care coordination and communication.<sup>9</sup>

**Quality:** 1) Quality equals patient outcomes.<sup>11</sup> 2) “..the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.”<sup>12,13</sup>

**Quality measure:** 1) Measures developed to support assessment of quality dimensions (e.g., health outcomes, care processes) at the provider, health sector and patient levels.<sup>14</sup> Synonyms: performance measures, quality indicators. 2) A mechanism to assign a quantity to an attribute by comparison to a criterion.<sup>2</sup>

**Quality Improvement:** “..the combined and unceasing efforts of everyone – healthcare professionals, patients and their families, researchers, payers, planners and educators – to make the changes that will lead to better patient outcomes (health), better system performance (care) and better professional development (learning).”<sup>15</sup>

**Structure:** A dimension of quality that addresses the setting in which health care takes place, including the facilities, qualified staff, and administrative / fiscal organization that support medical care.<sup>9</sup>

**Subjective health measures:** Outcome measure using inherently subjective patient (or clinician) assessment (e.g., patient’s report of the health condition, treatment, health-related quality of life, satisfaction with treatment).<sup>8</sup>

**Surrogate endpoint:** Use of a biomarker to substitute for a clinical outcome or endpoint; the biomarker is expected to predict clinical outcome based on epidemiologic, pathophysiologic or other evidence.<sup>1</sup>

**Validity:** The degree to which the measure reflects the construct that it was intended to measure rather than something else.<sup>16</sup>

**Value of health care:** 1) Health outcomes achieved per dollar spent.<sup>11</sup> 2) Benefits of treatment weighted against its financial cost.<sup>1</sup>

## **APPENDIX B**

### **Additional Tables and Figures**

**Table B1. Overview of Literature Searches**

<u>MeSH terms for PUBMED:</u>	<u>Key words for PUBMED and Web of Science:</u>
Outcome Assessment (Health Care)	Health outcome*
Outcome Assessment (Health Care)/Methods	Health-related outcome*
Outcome and Process Assessment (Health Care)	Health related outcome*
	Clinical utility
	Patient-reported outcome*
	Personal utility
	Outcome* framework
	Outcome* hierarchy
Genetics, Medical	Clinical genetics
Genetic Counseling	Genetic counseling
Genetic Services	Health care value
Genetic Testing	Value in health care
Genetic Diseases, Inborn	Value framework
	Quality framework

Limits:

English [Lang]

1990/01/01 [PDAT] : 2011/09/28 [PDAT]

Examples: An early MEDLINE search is shown below. This search returned 10,100 citations, not a realistic number for this review.

*("genetics, medical"[Mesh] OR "clinical genetics"[TW] OR "genetic counseling" [TW] OR "genetic diseases, inborn"[Mesh]) AND ("Outcome Assessment (Health Care)"[Mesh] OR "outcome\* assessment"[TW] OR "health outcome\*" [TW] OR "outcome\* hierarchy"[TW] OR "outcome\* framework"[TW]) AND English[Lang] AND "1990/09/28"[PDAT] : "2011/09/28"[PDAT]*

Because the majority of citations represented primary studies, many not related to genetics, we tried removing the broad MeSH term Outcome Assessment (Health Care). Another approach could have been to adjust the time frame of the search (e.g., to 2000 to 2011), but we did not know at that point how many of the articles we sought were published prior to 2000. The MEDLINE search shown below returned 419 citations; 19 were selected for further review and 16 of these articles were ultimately included. MeSH terms associated with citations of interest, as well as review of bibliographies, were investigated to continue to identify the types of information available, and the most effective terms for the staged searches.

*("genetics, medical"[Mesh] OR "clinical genetics"[TW] OR "genetic counseling" [TW] OR "genetic diseases, inborn"[Mesh]) AND ("outcome\* assessment"[TW] OR "health outcome\*" [TW] OR "outcome\* hierarchy"[TW] OR "outcome\* framework"[TW]) AND English[Lang] AND "1990/09/28"[PDAT] : "2011/09/28"[PDAT]*

**Table B2. Exclusion criteria overall and by key question (KQ)**

<b>Key Question</b>	<b>Criteria</b>
<b>All</b>	<p>English abstract; full article not available in English.</p> <p>Abstracts or summaries with no corresponding full document or published article.</p> <p>Articles / documents that do not provide information relevant to one or more key questions.</p> <p>Abstracts</p> <p>Opinions and Editorials will be excluded unless it is deemed by the reviewers to be an objectively presented and referenced proposal of a new idea, model or process.</p> <p>Primary research studies, unless part of a targeted search requested by the Committee.</p>
<b>KQ4, 5</b>	<p>Articles / documents solely reporting service measures.</p>
<b>KQ6</b>	<p>Articles / documents not providing information on specific economic models or metrics for value that is used in or relevant to genetic diagnosis or genetic services.</p> <p>Articles / documents on health care economics not providing information or study results most relevant to US health care issues (e.g., high-income countries in North America, European Union).</p> <p>Articles not providing information relevant to the selected model disorders or clinical scenarios.</p>

**Table B3. Web sites reviewed for information relevant to the Key Questions**

<b>Name of Organization</b>	<b>Web site URL</b>
Agency for Healthcare Research and Quality	<a href="http://www.ahrq.gov">http://www.ahrq.gov</a>
American College of Medical Genetics (ACMG)	<a href="http://www.acmg.net">http://www.acmg.net</a>
American Medical Association	<a href="http://www.ama-assn.org">http://www.ama-assn.org</a>
Center for Medical Technology Policy	<a href="http://www.cmtpnnet.org">http://www.cmtpnnet.org</a>
Centers for Medicare and Medicaid Services (CMS)	<a href="http://www.cms.gov">http://www.cms.gov</a>
Cochrane Collaboration	<a href="http://www.cochrane.org/">http://www.cochrane.org/</a>
College of American Pathologists (CAP)	<a href="http://www.cap.org">http://www.cap.org</a>
European Network for Health Technology Assessment (EUnetHTA)	<a href="http://www.eunethta.net/Public/Home/">http://www.eunethta.net/Public/Home/</a>
EuroGentest	<a href="http://www.eurogentest.org/">http://www.eurogentest.org/</a>
Food and Drug Administration (FDA)	<a href="http://www.fda.gov">http://www.fda.gov</a>
Institute of Medicine Reports	<a href="http://www.iom.edu/Reports.aspx">http://www.iom.edu/Reports.aspx</a> <a href="http://www.nap.edu/catalog">http://www.nap.edu/catalog</a>
National Health Service/National Institute for Health Research/UK HTA	<a href="http://www.hta.ac.uk/">http://www.hta.ac.uk/</a>
NHS Information Centre	<a href="http://data.gov.uk/dataset/quality-and-outcome-framework-achievement-data">http://data.gov.uk/dataset/quality-and-outcome-framework-achievement-data</a>
National Human Genome Research Institute	<a href="http://www.genome.gov">http://www.genome.gov</a>
National Institute for Health and Clinical Excellence (NICE)	<a href="http://www.nice.org.uk/">http://www.nice.org.uk/</a>
National Pharmaceutical Council	<a href="http://www.npcnow.org">http://www.npcnow.org</a>
National Quality Measures Clearinghouse, Agency for Healthcare Research and Quality	<a href="http://qualitymeasures.ahrq.gov/">http://qualitymeasures.ahrq.gov/</a>
Organisation for Economic Co-operation and Development (OECD)	<a href="http://www.oecd.org">http://www.oecd.org</a>
Pharmacogenetics & Pharmacogenomics Knowledgebase	<a href="http://www.pharmgkb.org/">http://www.pharmgkb.org/</a>
UK National Health Service	<a href="http://www.nhs.gov">http://www.nhs.gov</a>
World Health Organization	<a href="http://euro.who.int/en/home">http://euro.who.int/en/home</a>

**Table B4** Quality criteria for individual qualitative studies<sup>17-20</sup>

<b>General</b>	What is being studied and was sufficient detail provided? Whose perspectives were addressed?	Narrative
<b>Participants</b>	Was the selection of each group/population clearly described? Were the characteristics of the group(s)/population(s) adequately described? If method involved interview, did the participants provide detailed and expansive descriptions? Were the participants rights protected? Did the researcher eliminate bias?	Yes No Unclear NA for each question
<b>Sample</b>	Was it adequate? What is the setting in which the study was carried out and was it appropriate to acquire an adequate sample? Was the sampling method appropriate? Do the data accurately represent the study participants? Was saturation achieved?	
<b>Data collection</b>	How were the data collected? Were the tools adequate? Were the data coded? If so, how? How accurate and complete were the data? Does gathering the data adequately portray the phenomenon?	
<b>Results of the study</b>	Was the purpose of the study clear? Is the research design appropriate for the research question? Is the description of findings thorough? Do findings fit the data from which they were generated? Are the results logical, consistent and easy to follow? Were all themes identified, useful, creative and convincing of the phenomena? Are the findings transferable to other settings?	

Overall assessment of quality as *Good*, *Fair* or *Poor* will be determined based on the number and weight of study strengths and weaknesses.

**Good** No major features that risk biased results.

**Fair** Susceptible to some bias, but flaws not sufficient to invalidate the results.

**Poor** Significant flaws that imply bias of various types that may invalidate the results.



**Table B5.** Criteria for assessing quality of published or unpublished documents and web materials (not studies)<sup>21-23</sup>

<b>Relevance</b>	Is the document relevant to the review? Is the document relevant to a specific key question?	Yes No Unclear NA
<b>Purpose</b>	Was there a statement of purpose for a meeting, a defined charge for a committee, specified key questions for a systematic review or a reason for producing the document/web site?	
<b>Source</b>	Was the document from a reliable source (e.g., NIH or policy web site)	
<b>Target audience</b>	Was the target audience(s) identified?	
<b>Review</b>	Was there any information provided on review? Was there review at the expert or peer level?	
<b>Dating</b>	Was there a date published/posted? If relevant, had the information been updated after January, 2009?	
<b>Bias</b>	If an invited commentary/editorial/opinion, was the author(s) an expert in the field or otherwise qualified? Was the presentation of information balanced or was there a discernable point of view supported? Were there any potential conflicts of interest noted or declared?	
<b>Results</b>	Were results partly or wholly based on literature review? If conclusions were based on consensus, were minority viewpoints or alternative interpretations provided? Was sufficient information and discussion provided to allow readers to follow and understand conclusions? If recommendations were made, was the rationale clear?	
<b>Reviewer opinion</b>	Did you deem the document or website to be accurate and credible? If specific concerns, document in Access <i>ACMG Value</i> database.	

Overall assessment of quality will be: **Good:** Systematic review or document with internal and/or external expert or peer review, clear presentation of results based on literature and/or consensus (e.g., professional or advisory or committee reports).

**Fair:** 1) Document from reliable source (e.g., white paper, government web page) with clear information, authorship and/or target audience(s), but no information on level of review. 2) Otherwise *Good* quality documents with an observed weakness in one or more categories. 3) Invited commentary, editorial, opinion written by a known expert with the potential for bias.

**Poor:** 1) Web publication from source of unknown reliability, unclear target audience and/or no information on authors or review. 2) Invited commentary, editorial, opinion from a source with unclear relevant expertise and/or suspected bias. 3) Web page or document no clear authorship, references or dating.

**Table B6. Hierarchy of quality levels for assessment of qualitative findings for each key question** <sup>24,25</sup>

<b>Level of quality</b>	<b>Characteristics</b>	<b>Certainty</b>	<b>Examples</b>
Convincing	Generalizable information Shows diversity in perspective Provides clear indications for practice or policy, offers support for current practice, or critiques with indicated directions for change.	Findings that address specific questions and topics are have reasonable depth and diversity and are unlikely to change based on new information.	Published methods/processes reflecting diversity of experience
Adequate	Conceptual information Shows diversity in perspective Uncertainties should be clearly identified.	The available findings are limited in some way: Number or quality of data sources Inconsistency of findings	Mainly literature-based analyses of theoretical concepts that recognize diversity in perspectives
	Practical rather than theoretical information Descriptive May not show diversity in perspective <sup>1</sup> Demonstrates that a finding exists in a defined group and/or identifies issues for further consideration.	Limited generalizability of findings Lack of diversity; certain perspectives not adequately represented  As more information becomes available, changes in findings may alter conclusions and/or decision- making.	Mainly practical information from individual authors or a defined group or a focus on a specific sub-topic
Inadequate	Information from the views or experience of one person or specific group; does not look at applicability to other contexts.	The available findings are currently insufficient or limited in scope to address the questions or topics. More information is needed to support conclusions and/or decision-making.	Mainly commentary/editorial/ opinion or documents with a limited view and/or potential bias

<sup>1</sup> Note that “lack of diversity” could also simply reflect a specific focus

**Table B7.** Genetics-specific validated outcome measures (Payne et al., 2008, Table 2)<sup>8</sup>

**Coping**

- Psychological Adaptation to Genetic Information Scale

**Decision-making**

- Decision-making process
- Intent to act on shared decision-making program

**Expectations**

- Beliefs about Breast Cancer Genetic Testing
- Prostate cancer genetic screening survey
- Quality of Care through the Patients' Eyes

**Knowledge**

- Breast Cancer Genetic Counseling Knowledge Questionnaire
- Genetic Knowledge Index
- Knowledge about genetic testing for inherited cancer (HNPCC and breast cancer)
- Knowledge about genetic risk for breast cancer
- Measure of Counselors' Knowledge of Down Syndrome
- Modified Maternal Serum Screening Knowledge Questionnaire
- Risk comprehension/subjective knowledge of women in shared decision-making

**Outcomes of genetics service**

- Audit Tool for Genetic Services

**Perception of risk (benefit)**

- Assessment of benefits and risk of breast cancer testing
- Perceptions of the benefits, limitations, and risks of genetic testing

**Perceive personal control**

- Perceived personal control

**Personality profiles**

- Medical Communication Behavior System
- Desire to participate in the shared decision-making program

**Psychological impact**

- Anticipated impact of results
- Emotional reaction to the program information
- Health Orientation Scale

**Satisfaction**

- Genetic Counseling Satisfaction Scale
- Patient Satisfaction with Genetic Counseling
- Satisfaction with shared decision-making program rationale acceptability

**Self-esteem**

- Body Image/Sexuality Scale

**Worry**

- Breast cancer (hereditary) concern
- Multidimensional Impact of Cancer Risk Assessment
- Worry Interference Scale

**Table B8.** Complete Genetic Services Outcomes Menu (Silvey et al., 2009)<sup>26</sup>

Impact Area	Outcomes
<b>I. Knowledge and Information</b>	<b>A. General public</b>
	<ol style="list-style-type: none"> <li>1. Individuals and families have information about the impact of genetics on their or their family's health, and are able to make informed decisions based upon this information.</li> <li>2. Quality, culturally appropriate resources exist that assist individuals and families in understanding family health history; signs or symptoms of genetic conditions; screening and testing options and implications; diagnosis; treatment; and long-term follow-up.</li> <li>3. Parents are confident in communicating about familial genetic risk information with their children.</li> <li>4. Individuals or families know what genetic services they need and where to find them.</li> <li>5. Information about genetic research and clinical trials is available to families and integrated into clinical practice.</li> <li>6. Individuals and families participate in treatment at optimal levels after receiving counseling and education.</li> </ol>
	<b>B. Health care providers (HCPs)</b>
	<ol style="list-style-type: none"> <li>1. HCPs use current information about incidence; prevalence; epidemiology; diagnosis and treatment of genetic conditions to prevent, cure, and treat individuals with heritable conditions.               <ol style="list-style-type: none"> <li>a. HCPs integrate information about clinical trials/research into clinical practice.</li> <li>b. HCPs use up to date, diagnosis specific protocols that are available on the internet.</li> </ol> </li> </ol>
<b>I. Knowledge and Information</b>	<b>C. Others – public health agencies, insurers, legislators, researchers</b>
	<ol style="list-style-type: none"> <li>1. Federal and state legislators use current information about genetics to write laws that foster prevention, cure, and treatment of genetic conditions.</li> <li>2. Providers, payers, and employers have policies and procedures to ensure appropriate use of genetic information.</li> <li>3. Public health agencies have up to date information about incidence, prevalence and epidemiology of genetic conditions, and apply this knowledge to foster prevention, cure, and treatment.</li> </ol>
	<b>II. Financing</b>
<ol style="list-style-type: none"> <li>1. Financing for screening is adequate.</li> <li>2. Early and timely screening contribute to lower long-term diagnostic and treatment costs.</li> <li>3. Financing for diagnosis, health management and long-term care is adequate.               <ol style="list-style-type: none"> <li>a. Health insurers reimburse diagnostic and treatment services for genetic conditions. (from <i>Mandate for Quality Genetic Services</i>)</li> <li>b. Individuals and families have adequate private and/or public insurance to pay for services they need.</li> <li>c. Payers acknowledge psychosocial as well as physical effects of a genetic condition, on both the individual and the family, at each stage of life. (from <i>Mandate for Quality Genetic Services</i>)</li> </ol> </li> </ol>	
<b>B. Public health funding</b>	
<ol style="list-style-type: none"> <li>1. Funding is adequate at local and state levels to successfully carry out core public health functions and the ten essential public health services related to genetic conditions.</li> </ol>	

<b>III. Screening and Identification</b>	<b>1. Newborn screening, maternal serum screening</b>
	<ol style="list-style-type: none"> <li>1. All pregnant women receive prenatal counseling or screening for birth defects and genetic diseases.</li> <li>2. All infants have equal access to timely screening for genetic conditions.</li> <li>3. Parents of newborns learn about their babies' hearing status near the time of birth.</li> </ol>
	<b>2. Health care provide screening – risk assessment, family history</b>
	<ol style="list-style-type: none"> <li>1. Primary care providers continually implement risk assessment for genetic conditions for all patients in their practice.</li> <li>2. Children, adolescents and adults are screened early for special health needs that result from genetic conditions.</li> </ol>
	<b>3. Individuals – family health history</b>
	<ol style="list-style-type: none"> <li>1. Individuals and families learn of their genetic health risks in a timely and culturally appropriate manner.</li> <li>2. Individuals and families can share genetic risk information without fear of loss of insurance or employment.</li> </ol>
<b>IV. Diagnosis, Treatment and Management</b>	<b>A. Family centered</b>
	<ol style="list-style-type: none"> <li>1. Individuals and families are able to learn about a diagnosis of a genetic condition.</li> <li>2. Individuals and families are able to make informed health and life decisions based upon diagnosis.</li> <li>3. Individuals and families are able to better carry out treatment as a result of counseling and education.</li> <li>4. Individuals and families partner in decision-making at all levels, and are satisfied with the services they receive. (MCHB CSHCN Performance Measure)</li> <li>5. Individuals and families partner with their healthcare providers to identify needs, develop and monitor treatment plans, and manage their genetic condition. (from <i>Mandate for Quality Genetic Services</i>)</li> <li>6. Information about genetic conditions is provided to individuals and families in a culturally appropriate manner, which may include: primary language, appropriate educational level, and various media. (from <i>Mandate for Quality Genetic Services</i>)</li> <li>7. All newborns receive timely diagnosis and ongoing health management for at least three years after a positive newborn screen.</li> </ol>
	<b>B. Health care providers</b>
	<ol style="list-style-type: none"> <li>1. A continuum of health services from ambulatory care to long-term care for individuals with genetic conditions is available in their community.</li> <li>2. Individuals and families receive coordinated, culturally appropriate, ongoing comprehensive care within a medical home. (MCHB CSHCN Performance Measure)</li> <li>3. Services for individuals and families are organized in ways that families can use them easily. (MCHB CSHCN Performance Measure)</li> <li>4. Healthcare providers refer individuals to appropriate specialists, as needed, including those outside of their health insurance plan. (from <i>Mandate for Quality Genetic Services</i>)</li> <li>5. Primary care providers are able to obtain diagnosis for their patients with genetic conditions.</li> <li>6. Initial referrals to support groups and resources are offered at regular office visits. (from <i>Mandate for Quality Genetic Services</i>)</li> </ol>

<b>V. Population Health</b>	<b>A. Optimal growth and development through lifespan</b>
	<ol style="list-style-type: none"> <li>1. Individuals or families have optimal physical and psychosocial health related to their genetic condition.</li> <li>2. Symptoms or complications of genetic conditions are prevented or detected early.</li> <li>3. Individuals and families have improved diet and nutrition.</li> </ol>
	<b>B. Quality of life</b>
	<ol style="list-style-type: none"> <li>1. Individuals and families feel supported in managing grief, stress, and emotional challenges of living with a genetic condition.</li> <li>2. Individuals and families receive services necessary to make appropriate transitions such as to adult health care, work, employment, long-term care.</li> <li>3. Individual and family daily functioning is optimal.</li> <li>4. Time away from work is decreased.</li> <li>5. Need for urgent and emergency care decreases.</li> </ol>

**TABLE B9.** Examples of types of health-related outcomes (Botkin et al., 2010, Table 1)<sup>27</sup>

Potential Outcomes	Examples
<b>Diagnostic thinking/health information impact</b>	Ending diagnostic odyssey  Knowledge of prognosis/disease course Long-term planning Distress (increased or decreased) Satisfaction with testing services Increased/decreased sense of control Stigmatization or discrimination Incidental information (unwanted information) Changes in family dynamics Cultural, ethnic identity
<b>Therapeutic choice</b>	Changes in preventive or therapeutic strategies Adherence to therapeutic regimen Satisfaction with treatment choice Health behavior (test recipients)
<b>Patient outcome impact</b>	Mortality Morbidity Change in response to therapy Incidence of adverse outcome(s) after testing Severity of adverse outcome(s) after testing Health-related quality of life Pregnancy termination decisions Prenatal interventions
<b>Familial and societal impact</b>	Impact on health disparities Health care utilization by family members Disabilities perspective Fostering genetic determinism in society Eugenics attitudes in society Technology innovation Population health interventions

**Table B10.** Example of selecting and presenting outcomes of interest for a specific disorder/condition by outcome type that is pertinent to the patient and physician, as well as by relevance to the individual, family members, and society (Botkin et al., 2010, Table 2)<sup>27</sup>

**Table 2** Example outcomes matrix—testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with SSRIs

Outcomes	Rank	Outcome type		Outcome relevance		
		Patient outcome	Physician outcome	Individual level	Family level	Society level
<b>Diagnostic thinking</b>						
Knowledge of CYP	2		•	•		
Knowledge of risk	1	•	•	•		
Ability to interpret	1		•	•		
<b>Therapeutic choice</b>						
Selective use of SSRI	1		•	•		
Tailored dosage	1		•	•		
Time to dosage	2		•	•		
Adherence	2	•		•		
Changes in other drugs	3		•	•		
<b>Patient outcomes</b>						
<b>Morbidity</b>						
Short-term response	1	•		•		
Long-term response	1	•		•		
Incidence of AEs	1	•		•		
Severity of AEs	1	•		•		
Other med changes	3	•	•	•		
<b>Mortality</b>						
Incidence of suicide	1	•		•		
<b>Familial and societal impact</b>						
Economic evaluation	2					•
Reimbursement/access	2			•		•
Health disparities	3					•
Relationship to disparity	3					•

SSRI, selective serotonin reuptake inhibitor; CYP, cytochrom P450; AEs, adverse events; Rank, the relative rank of this outcome on a scale of 1 to 3 (most to least important); patient outcome, outcome is primarily relevant to the patient; physician outcome, outcome is primarily relevant to the physician; individual level, outcome is relevant on an individual level; family level, outcome is relevant at the family level; society level, outcome is relevant at a societal level.



**Table B11.** Classification of National Quality Measures Clearinghouse (NQMC) Quality of Care Domains by Intended Use<sup>2</sup>

Intended Use	NQMC Quality of Care Domains
Assess quality of care provided by health care professionals and organizations	<u>Process of care</u> – a health care service to a patient based on evidence of efficacy or effectiveness
	<u>Outcome of care</u> – health state of a patient resulting from health care
	<u>Access to care</u> – patient’s timely access to appropriate care
	<u>Patient experience of care</u> – patient’s report on observations of and participation in health care
Assess capacity of health care professionals and organizations to provide high quality of care	<u>Structure of care</u> – a feature relevant to the ability of a health care organization or clinician to provide health care
Monitor trends in use of services and population health – Not direct measures of quality of clinical care	<u>Use of service</u> – measures to assess encounters, tests, and interventions provided to persons defined by geographic location, organizational affiliation or other non-clinical characteristics, as well as the efficiency of service delivery
	<u>Population health</u> – the state of health of a group of persons defined by geographic location, organizational affiliation, or non-clinical characteristics

**Table B12.** Quality Outcome Framework (QOF) Domains<sup>28,29</sup>

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Clinical – 86 indicators across 20 clinical areas, including:

- Heart disease (16 indicators)
  - Stroke and transient ischemic attack (8)
  - Diabetes mellitus (17)
  - Cancer (2)
  - Asthma (4)
  - Atrial fibrillation (3)
  - Mental health (11 indicators)
- 

Organizational – 36 indicators

- Records and information
  - Information for patients
  - Education and training
  - Practice and medicines management
- 

Patient experience – 3 indicators

- Patient experience relating to length of consultations and access to physicians
- 

Additional services – 9 indicators

- Cervical screening, contraception, maternity services, child health surveillance
-

**Table B13.** Development and Characteristics of QOF Indicators<sup>29</sup>

Lester and Campbell<sup>29</sup> proposed that the ideal attributes of a quality indicator were:

- *Acceptability* - to those performing the assessment and those being assessed
- *Attributable* – Those being assessed must have control over the aspect of care defined by the indicator
- *Feasibility* – Valid indicator and consistent data are available and collectable
- *Reliability* – Measurement error (e.g., inter-rater variability) is low
- *Sensitivity to change* – Capacity to detect changes in quality of care
- *Predictive value* – Validated ability to predict quality of care outcomes
- *Relevance* – Assesses an identified gap between actual and potential quality of care

The authors also considered what constitutes an ideal QOF indicator, or makes it “QOFable”?  
They concluded that the clinical issue or area to be addressed should be:

- Common
- Clearly defined and diagnosed
- Significant in terms of morbidity and/or mortality
- Have an identified set of plausible indicators.

The indicators selected should be:

- Clearly defined
- Evidence-based
- Attributable to specific actions or interventions in clinical care
- Achievable by every physician, organization or other entity to be assessed (e.g., does not require a test or imaging procedure that is not uniformly available)
- Able to be extracted from available data sources in an unambiguous manner
- Lacking apparent unintended consequences

**Table B14.** Sample Framework for Defining the Target Population – A Step in Creating Performance Measures (Spertus et al., 2005<sup>30</sup>)

**1150 Spertus et al.**  
**ACC/AHA Methodology for Creating Performance Measures**

JACC Vol. 45, No. 7, 2005  
 April 5, 2005:1147–56

**TABLE 2. Sample Framework for Defining the Target Population**

Patient Characteristic Category	Definition	Acceptable Responses	Potential Data Sources	Comments
Age	Years alive	18–120, unless otherwise noted	Patient records	Because the ACC/AHA guidelines are typical for adult patients, these performance measures are, in general, meant for patients 18 years of age or older, unless otherwise noted to include pediatric patients. This field is best calculated from birth date and date care was provided if HIPAA regulations permit collection of the birth date. If not, age should be calculated and entered.
Gender	Sex	Female, male	Patient records	Because the ACC/AHA guidelines define practices that meet the needs of most patients in most circumstances, the performance measures will be for both men and women.
Principal diagnosis	Diagnosis most responsible for visit/admission	XXX.XX	Patient records, billing records	Consider including relevant ICD-9 codes that define the group of patients that are the focus of the study. For prospective implementations, clinical criteria (eg, positive troponin with clinical features consistent with MI) could be used.
Principal procedure	Primary procedure performed	XXX.X	Patient records, billing records	Consider including relevant CPT-5/ICD-9 procedure codes that define the group of patients that are the focus of the study.
Period of care	Duration of care being studied	X months, Y years, etc	Patient records, billing records	Define the time period over which quality will be assessed for the cohort of patients.
Period of observation	Duration of time during which care is measured	MM/YY–MM/YY	N/A	This is the time during which cases may accrue for the observed provider.
Other restrictions	Continuous enrollment, discharged alive, etc	XXXXX	Patient records, billing records	Define any other general restrictions that are needed (eg, if assessing outpatient care up to 6 months after a hospital discharge, then patients should be discharged alive and continuously enrolled for up to 6 months so that data are complete).

HIPAA indicates Health Insurance Portability and Accountability Act; CPT, Current Procedure Technology; other abbreviations as in Table 1.

**Table B15.** ACC/AHA Phases of performance measure development<sup>14,30</sup>

- Define the target population and observation period
  - Identify dimensions of care
  - Review and synthesize the literature
  - Define and operationalize potential measures
  - Select measures
- I. Determine measure feasibility
- Definition of a sample
  - Feasibility of measure (*e.g.*, validity, reliability and completeness of data sources)
- II. Measure performance
- Determine reporting unit
  - Determine number and range of measures
- III. Evaluate performance

**Table B 16.** Summary of Steps for Performance Measure Development<sup>30</sup>

**TABLE 1. Summary of Performance Measure Development**

Task	Description
<b>Phase I: Constructing Measurement Sets:</b>	
Task 1: Defining the target population and observational period	Develop a clear, concise, and implementable definition of the sample (eg, adults more than 29 years of age, discharged alive with a principal diagnosis of heart failure (ICD-9: 398.91, 402.01, 402.11, 402.91, 428.0, 428.1, 428.9), with a length of stay of at least 1 day, excluding patients with an AMI in the previous month continuously enrolled for 6 months after discharge.
Task 2: Identifying dimensions of care	Explicitly define each aspect of care that should be quantified to ensure a valid assessment of the most meaningful aspects of care. Potential dimensions include diagnosis, risk stratification and patient education, treatment, self-management, and reassessment of patient's health status.
Task 3: Synthesizing and reviewing the literature	Review published literature (including guidelines and other performance measurement systems) with a team of clinicians and researchers with expertise in meta-analysis.
Task 4: Defining and operationalizing potential measures	For each measure, determine which data sources are available and define the data elements needed to construct it (including period of care).
Task 5: Selecting measures for inclusion in the performance measures set	Present information based on tasks 1–3 to writing group and other relevant individuals, and put in place a formal mechanism to decide upon the measures that will be selected for inclusion.
<b>Phase II: Determining Measure Feasibility:</b>	
Definition of sample	Calculate sensitivity and specificity of selection criteria whenever possible. Document sources of case attrition (eg, medical record never sent, not continually enrolled, died during period of care). Develop an algorithm to assign patients to providers (eg, primary care provider, specialist) and validate the accuracy of the algorithm.
Feasibility of measures	Report validity, reliability, and completeness of collected data. If chart abstraction is used, then interabstractor reliability needs to be measured; if patient survey is used, then item and unit nonresponse must be measured. Data lags in identifying and surveying patients need to be assessed.
<b>Phase III: Measuring Performance:</b>	
Determining reporting unit	Determine at what level information will be reported (eg, physician-level data will typically require longer accrual period, even if only for internal monitoring).
Determining number and range of measures	Cost constraints may dictate how many measures can be measured. For quality improvement, how many measures will be evaluated and/or whether a combined measure is necessary will need to be determined.
Evaluating Performance	<i>Caution:</i> To determine whether a provider has "improved" care over time or whether a provider is sufficiently different from others, a sample size calculation that incorporates the relevant statistical features of the "test" (within- and between-provider variability, size of test, significance of test) should be undertaken.

ICD indicates International Classification of Diseases; AMI, acute myocardial infarction.

**Table B17.** Exclusion criteria for performance measure development<sup>14</sup>

**Appendix D. Sample Performance Measure Survey Form and Exclusion Criteria Definitions**

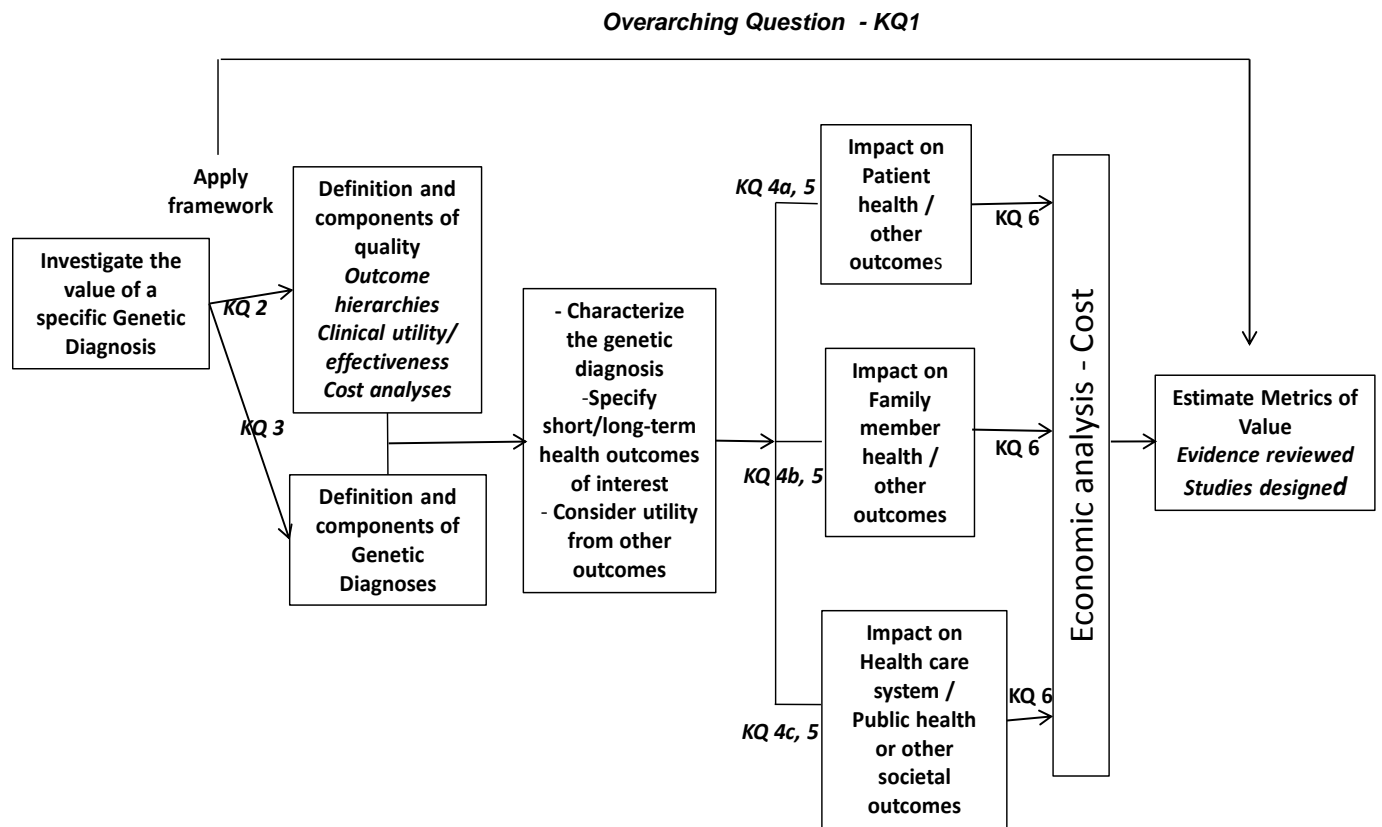
**PERFORMANCE MEASURE SURVEY  
EXCLUSION CRITERIA DEFINITIONS**

<b>Exclusion Criteria</b>	<b>Considerations</b>
<b>Useful in Improving Patient Outcomes</b>	
<b>1. Insufficient evidence:</b> The scientific basis for the recommendation is not well established.	Please note that ACC/AHA guideline recommendations with <b>Level of Evidence B</b> are based on limited evidence from a single randomized trial or nonrandomized studies, and recommendations with <b>Level of Evidence C</b> are only based on expert opinion, case studies, or standard of care. <i>Considering level of evidence, select this criterion if you find it appropriate to exclude a recommendation as a potential quality indicator.</i>
<b>2. Uninterpretable:</b> The degree to which a provider can clearly understand what must be done to successfully implement the recommendation.	
<b>3. Not actionable:</b> The recommendation addresses an area that is not under the practitioner’s control.	This is your assessment of the degree to which a provider is empowered to influence the activities of the healthcare system toward improvement.
<b>Useful in Measure Design</b>	
<b>4. Unclear patient population:</b> The patient group to whom this recommendation applies (denominator) is not clinically meaningful.	
<b>5. Not clinically meaningful:</b> The recommendation does not capture clinically meaningful aspects of care.	
<b>6. Uncertain reliability across settings:</b> The recommendation is not likely to apply across organizations and delivery settings.	
<b>Useful in Measure Implementation</b>	
<b>7. Uncertain feasibility due to effort:</b> The data required to measure successful implementation of the recommendation cannot be obtained with reasonable effort.	From your perspective, the required data can be typically abstracted from patient charts or readily available national registries or databases.
<b>8. Uncertain feasibility due to cost of data collection:</b> The data required to measure successful implementation of the recommendation cannot be obtained at reasonable cost.	
<b>9. Uncertain data collection period:</b> The data required to measure successful implementation of the recommendation cannot be obtained within the period allowed.	

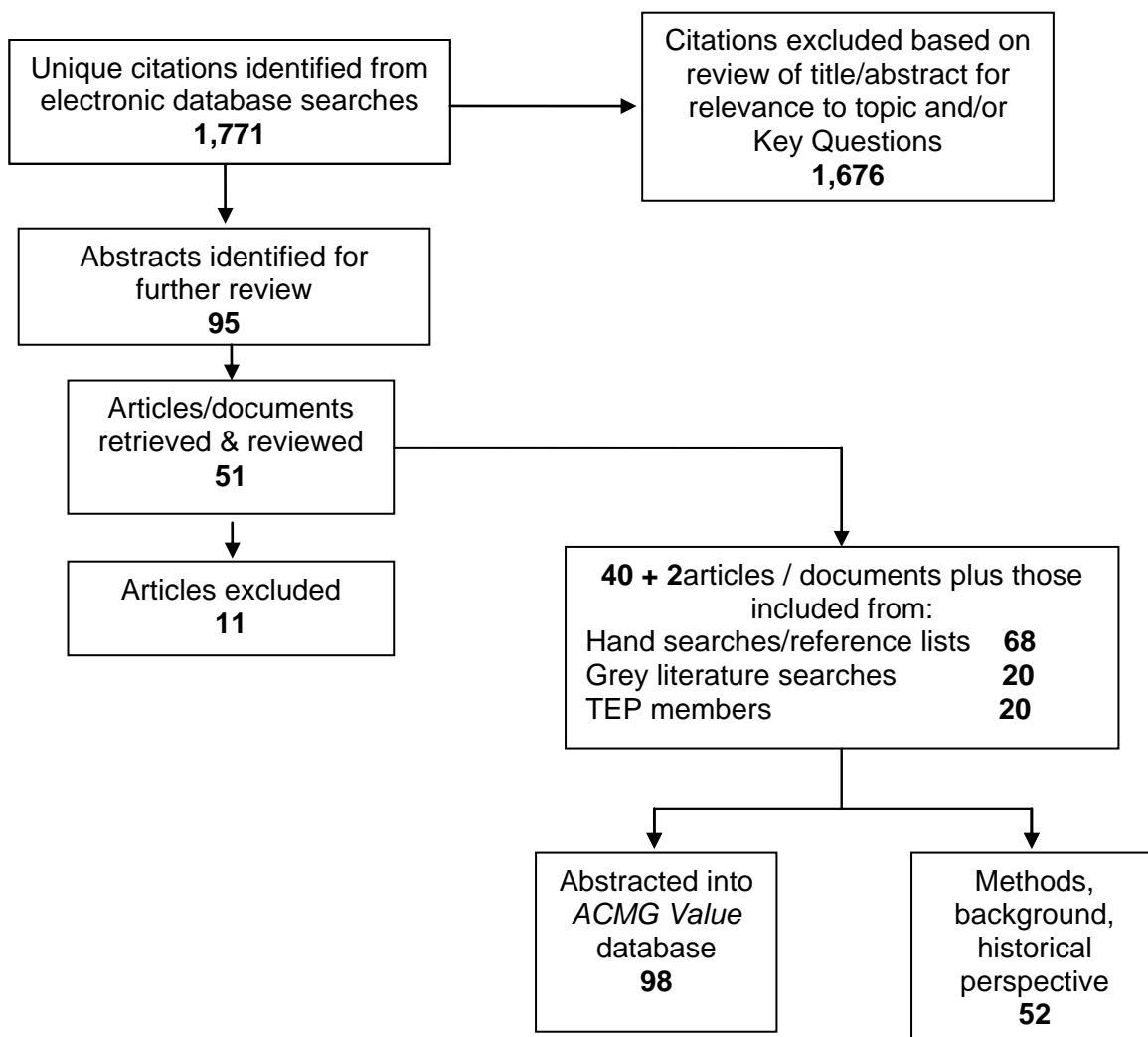
**Table B18.** Proposed 24 Question Genetic Counseling Outcome Scale (GCOS-24)  
(McAllister et al., 2011)<sup>31,32</sup>

- |  |  |
|--|--|
| 1. I am clear in my own mind why I am attending the clinical genetics service                                  | 13. In relation to the condition in my family, nothing I decide will change the future for my children/any children I might have |
| 2. I can explain what the condition means to people in my family who may need to know                          | 14. I understand the reasons why my doctor referred me to the clinical genetics service  |
| 3. I understand the impact of the condition on my child(ren)/any child I may have                              | 15. I know how to get the non-medical help I/my family need(s) (e.g. educational, financial, social support)                     |
| 4. When I think about the condition in my family, I get upset  | 16. I can explain what the condition means to people in my family who may need to know   |
| 5. I don't know where to go to get the medical help I/my family need (s)                                       | 17. I don't know what I can do to change how this condition affects me/my children   |
| 6. I can see that good things have come from having this condition in my family                                | 18. I don't know who else in my family might be at risk for this condition   |
| 7. I can control how this condition affects my family  | 19. I am hopeful that my children can look forward to a rewarding family life  |
| 8. I feel positive about the future  | 20. I am able to make plans for the future   |
| 9. I am able to cope with having this condition in my family   | 21. I feel guilty because I (might have) passed this condition on to my children   |
| 10. I don't know what could be gained from each of the options available to me                                 | 22. I am powerless to do anything about this condition in my family  |
| 11. Having this condition in my family makes me feel anxious   | 23. I understand what concerns brought me to the clinical genetics service   |
| 12. I don't know if this condition could affect my other relatives (brothers, sisters, aunts, uncles, cousins) | 24. I can make decisions about the condition that may change my child(ren)'s future/the future of any child(ren) I may have      |





**Figure B1. Review framework for the evidence review**




**Figure B2. Overview of literature search and selection of articles and documents.**

Note that later requested searches for genetic-disease specific outcomes are not included here, but the search strategies and identified articles are described in the narrative text (KQ4).

**Figure B3.** Example of an International Classification of Functioning, Disability and Health (ICF) Brochure by US Department of Health and Human Services

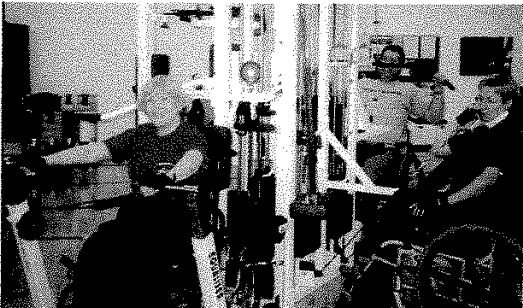
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## The International Classification of Functioning, Disability and Health (ICF)



### Individualized Exercise Prescriptions for People with Disabilities

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**What is the ICF?<sup>1</sup>**

The ICF provides a standard language for classifying health and changes in body function and structure. ICF helps identify how a person can function in a standard environment and in his usual environment. It differs from previously developed functioning assessments in that it accounts for environmental and personal factors.

**Who can use the ICF?**

The ICF is beneficial to health care providers, caregivers (including parents), and fitness professionals because it identifies factors that may prevent or enhance a person's participation in a specific physical activity.

**How do we use the ICF?**

Use the ICF like a needs assessment or as an outcome evaluation. By focusing on environmental and personal factors that result from or contribute to the individual's level of function and situation, a more personalized plan of action can be developed.

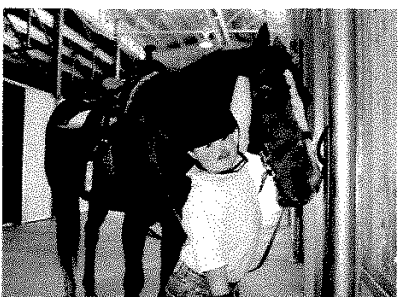
The ICF identifies three levels of functioning:<sup>2</sup>

- Body or body part
- Person
- Person in an environment or social context

**ICF Components<sup>2</sup>**

- \* Body functions are the physiological functions of body systems.
- \* Body structures are anatomical parts of the body such as organs, limbs, and their components.
- \* Impairments are problems in body function or structure such as a significant deviation or loss.
- \* Activity is the execution of a task or action by an individual.
- \* Participation is involvement in a life situation.
- \* Activity limitations are difficulties an individual may have in executing activities.
- \* Participation restrictions are problems an individual may experience in life situations.
- \* Environmental factors make up the physical, social, and attitudinal environment.

*The ICF emphasizes function,  
NOT the health condition, and  
categorizes the situation,  
NOT the person.<sup>1</sup>*

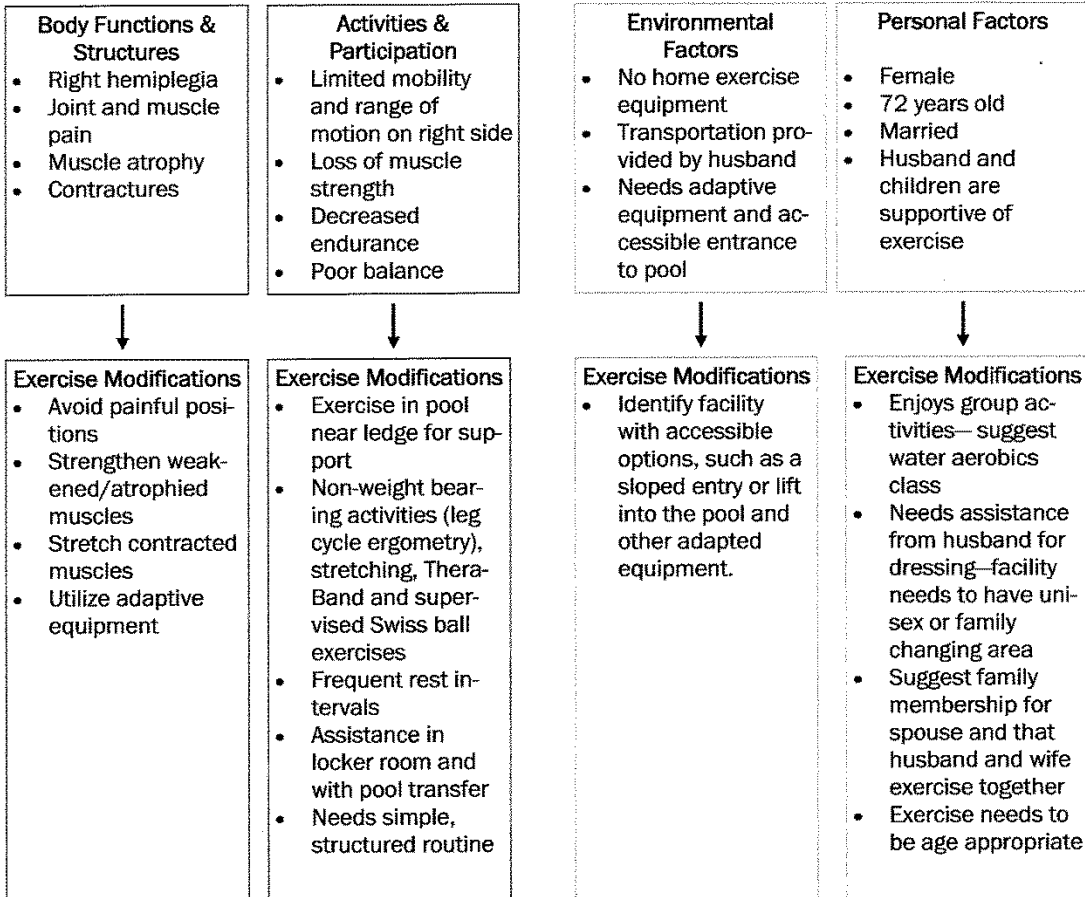


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## Application of the ICF: A sample assessment<sup>4</sup>

Purpose: Develop a cardiovascular rehabilitation plan

Health condition: Stroke survivor



### References

1. Use of the International Classification of Functioning, Disability and Health to prepare individualized exercise prescriptions for people with disabilities. [Electronic fact sheet]. (2006). Chicago, IL: National Center on Physical Activity and Disability [Producer and distributor]. Available from [http://www.ncpad.org/fitt/fact\\_sheet.php?sheet=459&view=all](http://www.ncpad.org/fitt/fact_sheet.php?sheet=459&view=all). Accessed June 18, 2007.
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### For More Information:

The President's Council on Physical Fitness & Sports  
 Voice: 202-690-9000  
 Online: [www.fitness.gov](http://www.fitness.gov)

The National Center on Physical Activity & Disability  
 Voice and TTY: (800)900-8086  
 Online: [www.ncpad.org](http://www.ncpad.org)

Figure B4. PROMIS Information<sup>33</sup>

**PROMIS Instruments Available for Use**

June 5, 2011

PROMIS has many assessment options available to measure self-reported health for clinical research and practice. PROMIS assessment instruments are drawn primarily from calibrated item banks (sets of well-defined and validated items) measuring concepts such as pain, fatigue, physical function, depression, anxiety and social function. These calibrated item banks can be used to derive short forms (typically requiring 4-10 items per concept), or computerized adaptive testing (CAT; typically requiring 4-7 items per concept for more precise measurement). Assessments are available for children and adults. Most PROMIS instruments are available through Assessment Center ([www.assessmentcenter.net](http://www.assessmentcenter.net)). Those which are not yet available on Assessment Center can be obtained by contacting the PROMIS Statistical Center through [help@assessmentcenter.net](mailto:help@assessmentcenter.net). Assessment Center can be utilized for online or offline computer-based administration or instruments can be downloaded for paper administration or entry into other data collection platforms.

Tables 1 and 2 list the calibrated item banks or scales, short forms, and profiles. **Item banks** are calibrated items from which a summary score can be obtained from a subset of items (i.e. via CAT or short form) whereas **scales** are calibrated items from which a summary score should be obtained only from the complete set of items. **Item pools** are collections of related items that are not intended to produce a summary score but instead are to be used as single items. Short forms are static subsets of item banks, and profiles are fixed collections of short forms measuring multiple concepts. Table 3 highlights instruments soon to be available in Assessment Center.

Table 1: PROMIS Instruments Available in Assessment Center ([www.assessmentcenter.net](http://www.assessmentcenter.net))

Domain	Adult - # items		Pediatric - # items	
	Bank/Scale	Short Forms	Bank/Scale	Short Form
Emotional Distress – Anger	29	8	6	
Emotional Distress – Anxiety	29	4, 6, 7, 8	15	8
Emotional Distress – Depression	28	4, 6, 8a, 8b	14	8
Applied Cognition – Abilities	33	4, 6, 8		
Applied Cognition – General Concerns	34	4, 6, 8		
Psychosocial Illness Impact – Positive	39	4, 8		
Psychosocial Illness Impact – Negative	32	4, 8		
Fatigue	95	4, 6, 7, 8	23	10
Pain – Behavior	39	7		
Pain – Interference	41	4, 6a, 6b, 8	13	8
Pain Intensity	3			
Physical Function	124	4, 6, 8, 10, 20		
– Mobility			23	8
– Upper Extremity			29	8
Physical Function for Samples with Mobility Aid Users	114	12		
Sleep Disturbance	27	4, 6, 8a, 8b		
Sleep-Related Impairment	16	8		
Sexual Function: Global Satisfaction with Sex Life	7			
Sexual Function: Interest in Sexual Activity	4			
Sexual Function: Lubrication	8			
Sexual Function: Vaginal Discomfort	10			
Sexual Function: Erectile Function	8			
Sexual Function: Orgasm (uncalibrated item pool)	3			
Sexual Function: Therapeutic Aids (uncalibrated item pool)	9			
Sexual Function: Sexual Activities (uncalibrated item pool)	12			

1

Sexual Function: Anal Discomfort (uncalibrated item pool)	5			
Sexual Function: Interfering Factors (uncalibrated item pool)	10			
Sexual Function Screener Questions (uncalibrated item pool)	3			
Satisfaction with Participation in Discretionary Social Activities (v1.0)	12	7		
Satisfaction with Participation in Social Roles (v1.0)	14	4, 6, 7, 8		
Satisfaction with Social Roles and Activities (v2.0)	44	4, 6, 8		
Ability to Participate in Social Roles and Activities	35	4, 6, 8		
Companionship	6	4, 6		
Informational Support	10	4, 6, 8		
Emotional Support	16	4, 6, 8		
Instrumental Support	11	4, 6, 8		
Social Isolation	14	4, 6, 8		
Peer Relationships			15	8
Asthma Impact			17	8
Global Health*	10			

\*The Global Health instrument is scored into a physical and mental health summary score.

Table 2: PROMIS Profile Instruments Available on Assessment Center ([www.assessmentcenter.net](http://www.assessmentcenter.net))

Domain	PROMIS-29	PROMIS-43	PROMIS-57
	# Items		
Emotional Distress – Anxiety	4	6	8
Emotional Distress – Depression	4	6	8
Fatigue	4	6	8
Pain – Interference	4	6	8
Pain – Intensity	1	1	1
Physical Function	4	6	8
Sleep Disturbance	4	6	8
Satisfaction with Social Participation (Social Roles v1.0)	4	6	8

Table 3: PROMIS Instruments Available from the Statistical Center ([help@assessmentcenter.net](mailto:help@assessmentcenter.net)) prior to Integration in Assessment Center

Domain	Adult # items Bank/Scale	Adult # items Short Form	Expected Integration in Assessment Center
Pain Quality (uncalibrated item pool)	56		2011
Parent Proxy	Item banks and short forms for Anxiety, Asthma Impact, Depressive Symptoms, Fatigue, Mobility, Pain Interference, Peer Relationships, and Upper Extremity		2011

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