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ACMG STATEMENT

Consideration of disease penetrance in the selection of secondary findings gene-disease pairs: A policy statement of the American College of Medical Genetics and Genomics (ACMG)

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Introduction

Patients, clinicians, and researchers are largely supportive of the return of secondary findings (SF) based on a curated list of actionable genes. Since 2014, the American College of Medical Genetics and Genomics (ACMG) Secondary Findings Working Group (SFWG) has been tasked with developing and implementing a framework for this curation process to maintain an updated gene list.

Two key data points related to actionability are penetrance, the likelihood that individuals with a specific

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variant will become affected, and expressivity, the likelihood that individuals will develop specific clinical features. Although these are 2 distinct genetic concepts, "penetrance" is commonly used incorrectly to refer to both. The question of how to incorporate penetrance data into the ACMG SF policy has been an important consideration for the SFWG since its inception. As Green et al[1] wrote in 2013 regarding consideration of penetrance as part of the SF process:

> "…we recognized that our clinical experience has been derived largely from patients with disease symptoms or positive family histories. As additional evidence accrues on the penetrance of these variants among persons without symptoms or family history, these recommendations will be expected to evolve."[1]

A decade later, considerable new data have, indeed, been generated. Our understanding of penetrance and expressivity has become more nuanced for certain genes, variants, and conditions, and our perspective as an ACMG working group continues to evolve. Here, we present the SFWG's current approach for the consideration of penetrance data in selecting gene-disease pairs for the SF list.

Historical origins

Thompson & Thompson Genetics in Medicine defines penetrance as "the probability that an allele or alleles will have any phenotypic expression at all" and expressivity as "the severity of expression of that phenotype among individuals with the same disease-causing genotype."[2] However, even among geneticists, the understanding and use of these terms is inconsistent at best, often used interchangeably, and sometimes applied to individual alleles, whereas at other times as properties of a gene or gene-condition pair.[3]

Part of this murkiness is perhaps explained by the fascinating, yet forgotten, 100-year history of the terms themselves. "Penetrance" and "expressivity" were originally coined by neuroanatomist Oskar Vogt in 1926. Most geneticists would be surprised to learn that these terms originate from the intersection of *Drosophila* experiments and human neuroanatomy research spurred by "a wishful program of establishing the genius embodied in V.I. Lenin's preserved brain."[4]

It is important to note that these concepts were first described to explain results specifically from individual alleles within inbred, maximally isogenic lines. Yet, even in the original 1926 article in which they were coined, Vogt blurs this distinction, leaping from penetrance as a property of specific alleles to a property of an entire gene. This lack of specificity was carried forward by Waddington, Dobzhansky, and others, appearing in genetics textbooks as early as 1950. In his seminal 1985 textbook, *Analysis of Human Genetic Linkage*, Ott defines penetrance as "the conditional probability R(xg) that an individual with a given genotype g expresses the phenotype x" as measured within a pedigree; this definition remains the standard.[5] The original context of isogenic lines was not discussed; by then, this history had already been lost to human genetics.

The rapid accumulation of patient genome, exome, and panel sequencing data in the modern era has even further blurred these definitions. Large-scale cohorts enable a genotype-first approach to ascertainment, facilitating the calculation of "population-based" penetrance across genes, conditions, and variants.[6-8] Yet, we use the same term "penetrance" relative to both gene-disease relationships and to individual genetic variants. One hundred years since they were coined, we are left with the same tension inherent in the terms' origins: penetrance and expressivity as properties of specific alleles in the context of family data (more isogenic) vs as properties of all variants within a gene, relative to a particular gene-disease pair, in the context of population data.

What, then, is the role of the ACMG SFWG in navigating and incorporating data relevant to these concepts?

SFWG consideration of penetrance

The ACMG SF recommendations must balance the potential benefits and harms of generating and disclosing a SF vs not generating a finding in the first place; our ability to predict risk in individuals with a SF is essential to this assessment. Thus, cutting through the semantic blur, inclusion of a nominated locus (gene or variant) on the SF list necessarily must consider the questions: (1) what is the likelihood that a person with this variant will develop disease? (2) Which disease features could they exhibit? (3) What is the evidence to support these conclusions?

In reflecting on the blurry and evolving nature of the term "penetrance" in the literature, and our experience reviewing nominations to date, the SFWG affirms the following principles in our consideration of penetrance:

1. Penetrance is 1 among several criteria

In reviewing each nomination, the SFWG weighs the estimated penetrance alongside other factors, such as phenotype severity, burden of potential treatments, etc. The SFWG also carefully considers the origin of any penetrance estimates when weighing against other factors—penetrance estimated from a limited set of families must be considered differently compared with estimates derived from genotype-first, population-scale approaches.[9] Figure 1 illustrates the totality of criteria considered by the SFWG for nominated genes or variants, including penetrance. In future iterations of the SF list, the SFWG will summarize the evidence considered for each gene-disease nomination alongside the workgroup decision. These evidence summaries will be presented in a way that is consistent with these discrete criteria, and consistent across nominated gene-disease pairs.

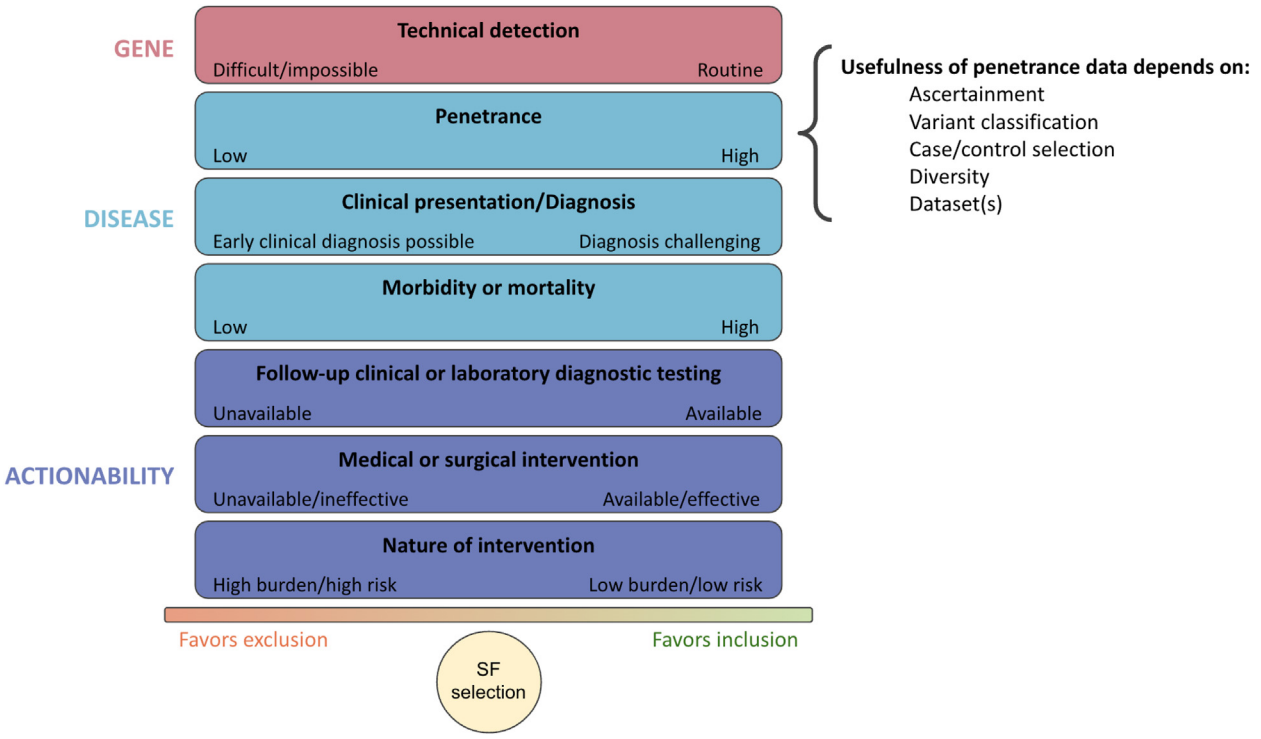

Figure 1 **Balancing different types of evidence for inclusion on the ACMG Secondary Findings List**.

2. Penetrance data derived from populations are the most directly applicable to SF list consideration, although not a strict requirement for inclusion

The clinical scenario most relevant to SF is an individual with a pathogenic or likely pathogenic variant but no previously recognized personal or family history for the associated condition. For this reason, population-based penetrance (ie, penetrance estimates obtained from a sample unbiased in terms of disease presence) is especially relevant to understanding whether a SF recognized through testing for another clinical purpose is likely to lead to a phenotype in the future. Ideally, penetrance estimates are (1) derived from population-scale cohorts in which any recruitment biases are acknowledged, (2) derived from genomic ascertainment in which variant classification for cases and controls is clearly documented, (3) stratified by sex and age, (4) presented with 95% confidence intervals and a clear methodology of derivation, (5) linked to a specific penetrant phenotype of interest, (6) derived from diverse cohorts, (7) provided from multiple sources, and (8) include cohorts with comprehensive clinical data/testing specific to the phenotype for the gene of interest.

3. Although evidence of high penetrance would support the inclusion of a gene or group of variants on the SF list, there is no strictly defined penetrance threshold for inclusion

Because it is just 1 among several factors, and because of the heterogeneity in the data and methods underlying penetrance estimates, the SFWG has not adopted, and does not plan to adopt, a strict penetrance threshold that nominated genes or variants must meet to be included on the SF list. Any such threshold would be chosen arbitrarily, derived from an evidence base that is incomplete and biased and could potentially exacerbate existing inequities in genomic medicine.

4. Generally, a higher penetrance threshold would be required to add a gene-disease pair when identification of a SF is likely to lead to a highly burdensome or risky intervention in asymptomatic individuals

Fundamentally, the goal of identifying SF is to intervene early to mitigate adverse health effects. In some cases, this goal can be achieved with noninvasive diagnostics, follow-up with a specialist, or other low-risk activities. Performing these types of interventions in individuals who will not go on to develop symptoms (because of low penetrance) might generate health care costs but are unlikely to generate significant medical harm. In other cases, preventing risk can only be achieved through surgery or another high-risk intervention. Performing these interventions in patients who would not have gone on to develop symptoms without intervention could create a net harm for such patients. This issue is a key reason that the SFWG is reticent to propose a specific penetrance threshold that would apply to all gene-disease pairs; the importance of penetrance in our decision making is a function of the risks introduced by interventions designed to mitigate genetic risk. It is important to note that consideration of these factors is always made in light of the expectation that a patient's health care provider(s) will do their best to use their professional judgment and shared

decision making to balance the risks and benefits of any intervention taken in response to the identification of a SF.

5. When there are differences in the penetrance or expressivity of a gene or group of variants among populations, workgroup decisions are guided by the principle of equity

Disparities in the diagnosis and treatment of genetic conditions persist despite recent efforts to address this challenge. Although the recognition of a SF does not guarantee that access to downstream care will be equitably distributed, it can at least help alleviate disparities in the recognition of patients who could be at risk. For this reason, genes or groups of variants with low frequency, penetrance, or expressivity at the total population level may still be considered for inclusion on the SF list if these factors are recognized to be elevated in underserved populations.

6. Our recommendations evolve with new data and updated guidance

Genotype-first ascertainment is an extremely valuable tool in understanding penetrance and expressivity and therefore in crafting SF recommendations. These data were critical in several gene-disease pair reevaluations, including *TTN*, *TTR*, and *HFE,* and allowed for the first variant-specific recommendations. We anticipate that similar data will continue to accumulate rapidly, and we have increased the SF list's release cadence to better reflect this evolving evidence.[10] We encourage the community to submit nominations for genes/variants to be added or removed from the list as these new data are generated.

We recognize that we are not the only expert workgroup grappling with the use of penetrance in clinical variant interpretation, and we will consider the guidance of these other groups, and their uptake by testing labs, alongside our recommendations. In particular, variants with known lower penetrance in genes that are also known to harbor high-penetrance variants present a challenge in the context of SF. Although they are "pathogenic" in the sense that there is confidence in their association with disease, the risk they confer is significantly lower and may not merit return in the context of SF. A recent recommendation from the Clinical Genome Resource Low-Penetrance/Risk Allele Working Group presents an updated classification framework for variants in this category, designating such variants as "risk alleles."[11] The most recent version of our policy states that only variants classified by the testing lab as pathogenic or likely pathogenic should be returned as SFs.[9,10] As testing labs' reporting practices regarding these risk alleles continues to evolve, we will consider this changing landscape in our ongoing task of maintaining the SF list.

Overall, these principles reflect a central tenet of the SFWG: a commitment to active consensus building and a rejection of algorithmic curation for this purpose. The careful consideration of many disparate criteria by a group with varying types of relevant expertise has led us to decisions unlikely to have been reached by such an algorithm, such as downweighting penetrance data in the context of severe potential outcomes (eg, *FLNC* and *TTN*) or known inequities in the literature and clinical practice (eg, *TTR*). Thus, the SFWG affirms that this process—manual review by an expert group that reflects the spectrum of ACMG members' expertise and opinion, with ad hoc contributions from experts in specific genes/conditions—is the most responsible way to maintain this list to benefit patients' health.

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Conflict of Interest

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