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January 5, 2016

Jerry Menikoff, MD, JD
Office of Human Research Protections
US Dept. of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

RE: Comments on Docket No. HHS-OPHS-2015-0008; Notice of Proposed Rule Making to Revise the Common Rule

Dear Dr. Menikoff:

The American College of Medical Genetics and Genomics (ACMG) is pleased to have the opportunity to comment on the proposed changes to the Common Rule. ACMG has significant interests in the proposed changes that relate to the involvement of its membership in rare disease genetics, its implications for families, and in the Public Health programs that have been developed to deliver genetic screening for presymptomatic newborns through newborn screening (NBS). In particular, through an NIH contract to ACMG, we operate the NICHD/NIH-funded Newborn Screening Translational Research Network (NBSTRN) through which infrastructure and resources have been developed to support research and quality improvement related to NBS.

General Comments

ACMG is supportive of the comprehensive approach that OHRP has taken in developing the proposed rule. However, we also have significant concerns about issues related to proposed changes on rare genetic diseases and, in particular, with the disconnect between the mechanisms by which individual autonomy is enabled vs. the importance of research in a time of rapid advancements in science and public health. The same issues that we commented on 2011 remain of concern. Throughout federal agencies, there has been a recognition of the difficulties faced by rare disease patients in the development of diagnostic tests and orphan drugs. Both required recognition that there is not a bright line between clinical research, translational practice, and the practice of the medical standard of care. It is also important to note that the US healthcare system remains rife with deep and wide chasms between public and private health care systems that vary across the states and wide variability in the capacities between small community hospitals and large tertiary care centers. Overreaching requirements could stifle data sharing efforts at a critical time. Lastly, it is important to note how CDC guidelines distinguish between public health research and public health service. In the context of population level public health work, the characterization of local and state

populations to inform analytical and clinical test performance is a part of test implementation after public health authorities have mandated that a particular condition be the target of screening.

ACMG recognizes the importance of individual autonomy in the use of one's identifiable information or biospecimens. Our hope is that a practical balance between the need for autonomy and the importance of creating a learning healthcare system driven by using individual level data and biospecimens for continuous improvement for all can be reached. Requirements for opt-in forms of consent in large populations are challenged by tradeoffs between the need for written consent and the need for those signing to be informed and the risks. Evidence suggests that when working at broad population levels, we risk losing representation of some subpopulations challenged by language or other issues. In considering these tradeoffs, we will have to be cognizant of the problem that is being addressed. In the context of newborn screening, it appears that the risks to individuals from their anonymous/deidentified involvement in the implementation of NBS is minimal and examples of harm to individuals are absent. We must align our consent policies with the magnitude of risks from which we intend to protect people so we don't overburden one of the most valued of public health programs.

A requirement to obtain parental consent for the future research use of DBS may limit the ability of state newborn screening programs to fulfill the requirements necessary for a condition to be added to the RUSP. The experience of the California state newborn screening program obtaining parental consent to implement a pilot supplemental screening program suggests that a sufficient number and type of DBS will not be available for new newborn screening test development if there is a requirement to obtain parental consent for future research use of DBS. Between January 2002 and June 2003, in response to a legislative mandate, the California Department of Health Services conducted a statewide pilot study to evaluate the effectiveness of using tandem mass spectrometry (MS/MS), a new technology, in newborn screening. The pilot study offered newborn screening for an expanded number of conditions. The pilot was designed as a research protocol, and parental informed consent was required to participate in the study.

Obtaining parental consent for use of DBS in secondary research is not as simple as obtaining consent from infants' parents. Hospitals and birthing centers must also agree to participate in obtaining consent. In the California MS/MS study, hospital participation varied widely. Twenty percent (n=63) of the hospitals in the state refused to participate, and none of the infants born in those hospitals were invited to participate in the study. Only 23% of hospitals offered the supplemental screening to greater than 75% of newborns. Overall, of the 755,698 babies born in California during the study period, only 52% were invited to participate, and only 47% agreed to participate. (L. Feuchtbaum, F. Lorey, J. Sherwin, et al., "California's Experience

Implementing a Pilot Study of Newborn Supplemental Screening Program Using Tandem Mass Spectrometry," *Pediatrics* 2006 May; 117 (3 Pt. 2): S261-9)

If hospitals refuse to seek consent from parents for retention and future use of their children's DBS, it is likely that significant portions of a state's population will not be included. If hospital participation varies by the ethnicity of the patients served, the DBS that are available for secondary research use will not be representative of the state's population, and results of research conducted using these samples will be biased. A representative sample is necessary to ensure that the test accurately reflects the members of the target population. The potential bias of this data raises serious concerns about justice and whether state newborn screening programs will be able to meet the needs of state populations, particularly if new newborn screening tests are not evaluated in specific sub-populations prior to the implementation of the new newborn screening test.

In addition to hospitals and birthing centers having to agree to seek parental consent, a sufficient number of parents must agree to participate in order to have sufficient numbers of DBS available for new newborn screening test development. Preliminary data from Texas and Michigan, where informed consent is sought for the future research use of DBS, suggest that approximately 65% of parents agree to the retention and future research use of their children's DBS. Many of the disorders included in the RUSP are rare (i.e. phenylketonuria has an incidence of 1 in 10,000-15,000 births, SCID 1-2 in 100,000 births). If only 65% of parents agree to allow the use of their children's DBS, it may become nearly impossible to evaluate the efficacy of new testing modalities for rare conditions, particularly in state with low birth rates.

If the ability of state public health departments to develop new newborn screening tests is hampered, we risk re-fragmentation of the newborn screening system and replacement of state newborn screening programs with testing offered by private companies, which may limit access for those unable to pay for the cost of these services. The development of a more robust parallel private system ultimately likely would threaten the state run newborn screening programs if private companies can offer better services, but the privatization of this important public health function would raise additional justice issues if access to these services is limited by the ability to pay.

Specific Comments

Question 1: Whether the proposed changes will achieve the objectives of (i) decreasing administrative burden, delay, and ambiguity for investigators, institutions, and IRBs, and (ii) strengthening, modernizing, and making the regulations more effective in protecting research subjects.

We are concerned that the proposed processes will stifle public health research and quality improvement when employed at the population level. The great majority of individuals involved in public health surveillance and detection programs such as newborn screening will screen negatively for the conditions targeted by the screening. Opt-in forms of consent will require that poorly informed staff in local birthing centers inform patients/families, will have limited capacity to answer questions, and will focus on acquisition of the signature.

Questions 2 and 3:
2. Would providing a definition of biospecimen be helpful in implementing this provision? If so, how might the definition draw a line between when a biospecimen is covered by the Common Rule, and when processing of biological materials (e.g., to create a commercial product used for
treatment purposes) has sufficiently altered the materials so that they should not be subject to the regulations? Would only covering biospecimens that include nucleic acids draw an appropriate line?
3. To what extent do the issues raised in this discussion suggest the need to be clearer and more direct about the definition of identifiable private information? How useful and appropriate is the current modifier ''may be readily ascertained'' in the context of modern genomic technology, widespread data sharing, and high speed computing? One alternative is to
replace the term ''identifiable private information'' with the term used across
the Federal Government: Personally identifiable information (PII). The Office of Management and Budget's 45 concept of PII refers to information that can be used to distinguish or trace an individual's identity (such as their name, social security number, biometric records, etc.) alone, or when combined with other personal or identifying information which is linked or linkable
to a specific individual, such as date and place of birth, mother's maiden name, etc. It is acknowledged that replacing ''identifiable private information'' with ''PII'' would increase the scope of what is subject to the Common Rule. However, the practical implications of such an expansion, other than the need to ensure that the data are security stored and otherwise protected against disclosure, may be minimal. Public comment is requested on the advantages and disadvantages of such a change.

ACMG acknowledges that an individual's DNA can identify them. However, this requires access to information commonly put into the public domain by the same individuals or through acquisition of a biospecimen known to have originated from that individual. We think it important that there be strong penalties in place for those violating an individuals privacy and autonomy.

Question 4: Which of the three proposals regarding the definition of human subjects achieves the most reasonable tradeoffs between the principles of autonomy (including transparency and level of trust) versus beneficence (as measured by facilitating valuable research)?

The purpose of changing the definition of human subjects to include biospecimens regardless of identifiability is to bring biomedical research conducted with biospecimens under the purview of the Common Rule and require some level of consent for the use of these specimens. The rationale for including all biospecimens, regardless of their identifiability, is that all biospecimens that contain DNA are inherently identifiable. However, the crux of the issue regarding the secondary use of biospecimens involves control over the use of information /specimens that make each individual unique. Therefore, application of the Common Rule to all biomedical research conducted with biospecimens is overly broad. The protections of the Common Rule are not necessary, for example, for research conducted to evaluate the electrolyte composition in de-identified blood samples. The inclusion of all biospecimens in the definition of human subjects would significantly alter how biomedical research is conducted in this country and would stifle if not prevent much of the research that currently is being conducted with very little additional benefit or protections to individual research participants.

Although autonomy is a laudable goal, transparency regarding the research use of biospecimens is paramount. In the newborn screening context, a perceived lack of transparence regarding the secondary use of DBS has been problematic. Even more important than autonomy will be transparency regarding how samples are used and the knowledge that there is some oversight of the research that is being conducted using these samples.

This definition would hinder the development of new newborn screening tests. Although it would increase parent autonomy over the use of their children's DBS, it would strike an improper balance between autonomy and the facilitation of valuable research. Although respect for persons would be enhanced if parental autonomy over the use of the samples is increased, there have been no demonstrated harms to infants or their families from the secondary research use of DBS, and the increased autonomy would come at significant cost in that the development of new newborn screening tests would be hampered. The increase in autonomy would not lead to decreased harm since there has been no harm and would jeopardize important public health activities.

Either of the two alternative definitions would be a better option than defining human subjects as including all biospecimens. Of the two alternatives, Alternative B would most likely achieve the goal of covering the portions of a biospecimen that make an individual unique. Further clarification of this definition would be necessary. Of particular importance would be spelling out how much information is necessary to make the information produced likely to be unique to the individual. For example, in some instances of "private" mutations, there are mutations that have been seen in only one individual in the world. In this case, information about a single

mutation would be enough to make the information unique to that individual. If this definition of human subjects is to be adopted, it will be important to draw bright lines about what information is included and what is not included to provide the research community with guidance regarding what types of activities are covered by the Common Rule.

In the context of rare diseases, ACMG believes that the translational practice of medicine not be conflated with research.

Question 7: Public comment is sought for whether biospecimens should not be included in any of these exclusion categories, and if so, which ones.

The first exclusion proposed in the NPRM at Section 101 (b)(1)(i) is for data collection and analysis, including the use of biospecimens, for an institution's own internal operational monitoring and program improvement purposes, if the data collection and analysis is limited to the use of data or biospecimens originally collected for any purpose other than the currently proposed activity. This exclusion permits the use of DBS for newborn screening program quality improvement and quality assurance activities. We support this exclusion because the continued successful operation of state newborn screening activities requires the use of DBS of both affected and healthy newborns for these purposes. For this reason, biospecimens SHOULD BE INCLUDED in this category.

Question 9: Public comment is requested on whether the parameters of the exclusions are sufficiently clear to provide the necessary operational guidance, or whether any additional criteria or parameters should be applied to clarify or narrow any of these exclusions.

The fifth category of excluded activities involves public health surveillance activities, including the collection and testing of biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority and limited to those necessary to allow the public health authority to identify, monitor, assess, or investigate potential public health signals….. including trends, or signals, and patterns in diseases….. or conditions of public health importance, from data, and including those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health, including natural or man-made disasters. (Section 101 (b)(1)(v). The NPRM notes that "public health surveillance refers to the collection, analysis, and use of data to target public health prevention."

Further clarification of the parameters of this exclusion is necessary to make clear which of the activities related to the development of new newborn screening tests are covered by this exclusion. The U.S. Centers for Disease Control and Prevention (CDC) has defined public health surveillance as "The systematic, ongoing, collection, management, analysis, and interpretation of data followed by the dissemination of these data to public health programs to stimulate

public health action."[i] The CDC clarified the distinction between surveillance and research by noting that "surveillance is used to gather data and knowledge that can be used to identify and control a health problem or improve a public health program or service, whereas the purpose of research is generalizable knowledge."[ii] Activities designed to develop new newborn screening tests clearly are designed to improve the state newborn screening program, a public health program and therefore fit within this definition.

Newborn screening is a public health program that is a hybrid of laboratory and clinical components. The purpose of the laboratory component is to identify infants at increase risk of disease in order to prevent or ameliorate the manifestations of the condition. This purpose is secondary prevention of disease. The laboratory component involves identification of at risk infants so that they can be transferred to the clinical care component of the newborn screening program for diagnostic testing, treatment when appropriate, and long-term follow up.

Certain activities related to the development of new newborn screening tests are part of the public health function of newborn screening programs and therefore should fall within the public health surveillance exclusion. For example, activities designed to establish reference ranges for new conditions within a specific population should be considered to be surveillance. The information would not be generalizable to other newborn screening programs due to differences in laboratory operations and population differences. Each laboratory would have to determine appropriate reference ranges within its own population. Similarly, the initial development of a new newborn screening test in a public health laboratory or in a research laboratory that is collaborating with a public health program should fall under the public health surveillance exclusion. Analytical validation of a stable newborn screening method or test system, including validation of a laboratory-developed test (LDT) or home brew and verification of an unmodified FDA-cleared or FDA-approved test system to establish performance specifications of a method per CLIA requirements also should fall within this exclusion. These activities are a necessary prerequisite to the performance of the public health function of newborn screening and should fall within the public health surveillance exclusion.

Other activities that should fall within the exclusion are determination of clinical validity of an analytically validated newborn screening method or test system. Clinical validity represents the accuracy with which the NBS test developed by that particular laboratory identified a patient's clinical status within that state's population and monitors statistical measures of the performance of the test which include: test sensitivity and specificity, true and false positives, true and false negatives, positive and negative predictive values. These activities are public health surveillance activities. The establishment of clinical utility also is a public health surveillance activity in this context. Clinical utility establishes the risks and benefits resulting fro the use of the newborn screening test in that population. This requires long-term follow-up and monitoring the impact of testing on patients. The state newborn screening program must

perform these surveillance activities to track the performance metrics of the existing program and the performance of new newborn screening tests.

At the very least, activities related to the implementation of a new newborn screening test for a condition for which screening has been mandated by the state should be included in the public health surveillance exclusion. The primary intent of these activities is to take the steps necessary to implement screening for a new condition as mandated by the state. DBS from known affecteds, lab created specimens, and anonymized DBS may be used for these activities as described in the SCID example above. The primary intent of these activities is not to create generalizable knowledge but to carry out the state mandate. The result of the state mandate is that screening for the new condition is now part of routine screening in these situations. If these activities are not excluded from the proposed Common Rule requirements, the state newborn screening program will be placed in the untenable position of having to obtain parental consent to evaluate the efficacy and utility of the inclusion of the new condition on the state newborn screening panel for a condition that is already included on the state panel. A requirement to obtain consent to evaluate the efficacy and utility of screening for a condition that has already been mandated by the state for the inclusion on the state newborn screening panel would be counterproductive and may undermine the state newborn screening program. Seeking consent for evaluation of a test for a condition that is already included on the state newborn screening panel could lead parents to refuse newborn screening and thereby place their infants at risk.

Clarification of the parameters of the public health exclusion is necessary so that state newborn screening programs will be able to undertake the activities necessary for new test development. If the parameters are not clarified, given the past controversies associated with the retention and secondary use of DBS, many state newborn screening programs may not undertake activities for which they have not been given express permission.

Question 54: Public comment is sought on whether the NPRM's proposal of exemption Section 104(f)(2) is the best option, or whether there is a better way to balance respect for persons with facilitating research.

This exemption is for research involving the use of biospecimens or identifiable private information that have been stored or maintained for secondary research use, if consent for the storage and maintenance of the information and biospecimens was obtained as detailed using the broad consent template that the Secretary of HHS will develop. For the reasons described above, this exemption should NOT be applicable to the use of DBS for new newborn screening test development. Rather, the public health surveillance exclusion should apply to the use of DBS for this purpose. However, if the parameters of the public health exclusion do not include the development of new newborn screening tests and consent for the secondary research use of DBS is to be required, this exemption for research involving DBS if broad consent for the

storage and maintenance of the DBS has been obtained is a better alternative than requiring specific consent for each individual research project.

If the public health surveillance exclusion applies to the development of new newborn screening tests, this exemption still may be appropriate for other types of secondary research use conducted using DBS.

We also have serious concerns about the implementation of this exemption. In the context of newborn screening, health care providers involved in the clinical care of newborn infants and their mothers would be the individuals required to seek parental consent for the storage and future secondary use of DBS. As discussed above in the California tandem mass spectrometry pilot study, many hospitals and hospital personnel may be unwilling to assume this responsibility. State newborn screening programs do not have the resources to send personnel to individual institutions to seek parental consent. The establishment of procedures for birthing centers to obtain consent is a significant hurdle in the implementation of these provisions. If parental consent is required to use DBS in the development of new newborn screening tests, and many hospitals are unwilling to seek consent, the development of new newborn screening tests may not be possible in the future in many states. I acknowledge that the challenges associated with the implementation of this exemption likely will have a similar effect on other types of research that may be conducted with DBS, but the development of new newborn screening tests should be differentiated from other types of research and while this other research may be valuable, priority should be placed on ensuring that new newborn screening test development can continue.

Question 55: Public comment is sought on whether and how the provision regarding the return of results in the proposed exemption should be revised.

The idea that an investigator could learn something about an individual that might be important to that individual's health and not be allowed to provide the individual with this information is profoundly disturbing. Rather than a blanket prohibition on returning results if research is conducted under a blanket consent and only allow return of research results if specific consent is obtained, a more reasonable approach would be to include in the consent document information that research results may be returned to participants if researchers learn something that might be important to the participants health. Alternatively, there should be a mechanism by which investigators could go back to an Institutional Review Board to seek permission to contact participants to provide them with information that might be important to their health. In this way, the IRB would have a role in determining which research results should be returned to participants and under what circumstances. In addition, many research participants may have an expectation that research results important to their health will be returned to them. If research results that may be important to their health are returned to them, the expectation of these participants can be fulfilled.

Question 65: Public comment is sought on how the waiver criterion regarding practicability at Section 116(d)(3) could be explicitly defined or otherwise clarified.

The development of new newborn screening tests using DBS presents unique challenges. Newborn screening represents a partnership between state public health programs and public and private hospitals, birthing centers, mid-wives, and others. Laboratory testing is conducted by state newborn screening programs, but these programs rely upon individual institutions and health care providers to ensure the timely collection of samples. As described above, many of these institutions and individuals may be unwilling to add to their burdens by seeking consent for the storage and secondary research use of DBS.

The practicability of obtaining consent for the storage and secondary research use of DBS is problematic not just from the standpoint of obtaining sufficient numbers of DBS to be useful but of obtaining consent for the storage and use of the requisite numbers of DBS from within particular populations. This issue is particularly problematic in the context of newborn screening test development for two reasons as described above. First, previous experience from California and more recent experience from Texas and Michigan suggests that many parents may refuse to consent to the retention and use of their children's DBS. Second, these refusals may result in possible bias that may result in certain populations not being included. These challenges may be exacerbated in states with a lower number of births per year or for test development of rare conditions.

Consider a state with a birth rate of 250,000 infants per year. The state newborn screening program would receive approximately 5,000 samples to screen each week. With a rare disease like Krabbe disease, in which there is no prior population screening data, with an incidence of approximately 1 in 100,000 newborns, the state may need to screen approximately 160,000 newborn to detect one affected infant. If 5000 samples are screened each week, 32 weeks of screening would be necessary to accumulate the data necessary to implement statewide screening for the condition.

If the state needed to obtain consent, and the consent rate is 65%, then the parents of a total of 246,000 infants would need to be asked for consent in order to obtain consent from 160,000 parents (65% of 246,000 is approximately 160,000). At a consent rate of 65%, it would require 49 weeks (an additional 4 months) to obtain the requisite number of samples. For many states, the additional resources required for this additional time would make test development impossible under this scenario.

Further clarification of the term "practicable" is necessary. For the purposes of newborn screening test development, the establishment of a threshold of incidence of disease may be useful in determining the level at which obtaining consent becomes impracticable. Obtaining

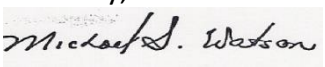
consent for the use of DBS in the development of new newborn screening tests for rare conditions with incidence less than the threshold could be considered impracticable, and under these circumstances, consent could be waived.

ACMG believes that OHRP should:

- Allow broad consents for future unspecified research use;
- Clear exclusion of new technology uses for which predicate standard of care testing platforms, devices and tests exist for comparison of test performance;
- The broad term of research not be applied to rare disease applications because the rarity of the conditions precludes robust statistical calculations of clinical validity and utility.
- Use of dried blood spots by pubic health programs to improve the quality of the service they provide to their entire population.

ACMG is grateful for the opportunity to comment on the questions facing the OHRP.

Sincerely,



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