Discussion Paper

Evaluating the Clinical Utility of Genomic Variants Derived from Next-Generation Sequencing for Opportunistic Disease Screening and Risk Assessment: Evidence Gaps and Priorities

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The types of evidence needed to support the use of genome sequencing in the clinic varies by stakeholder and circumstance. In this IOM series, seven individually authored commentaries explore this important issue, discussing the challenges involved in and opportunities for moving clinical sequencing forward appropriately and effectively.

Evaluating the Clinical Utility of Genomic Variants Derived from Next-Generation Sequencing for Opportunistic Disease Screening and Risk Assessment: Evidence Gaps and Priorities

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SUMMARY OF THE ISSUE AND ITS IMPORTANCE FOR PRACTICE

Next-generation sequencing (NGS; that includes whole exome or genome) is increasingly used in the diagnosis and management of suspected Mendelian diseases of unknown cause (germ line) and in precision medicine approaches to cancer treatment (somatic). As a result of such use of this technology, additional information derived from assessed genomic variants can be used for health screening or risk assessment purposes unrelated to the initial testing indication. The clinical utility of genomic tests has been assessed as the balance of benefits and harms (Teutsch et al., 2009) for the use of the test in its primary indication (e.g., workup of suspected genetic diseases). NGS methods provide a unique opportunity to use additional information on genomic variants (incidental findings) to screen for current asymptomatic disease or future risk of disease (e.g., BRCA mutations for breast/ovarian cancer). Such opportunistic screening could be examined under the rubric of "population screening," which may include other indications for looking at genetic variations, such as the context of family health history for various diseases and ethnic backgrounds.

We explore here evidence gaps and requirements for use of incidental findings for the purpose of opportunistic disease screening and risk assessment, for example, in screening for mutations associated with cancer, heart disease, and diabetes and possibly including other contextual factors, such as family history and ethnic background. This topic is of considerable importance for both practice and policy because genomic information can be used to supplement or modify existing guidelines on population screening for various diseases. For example, for variants with known high penetrance and clinical actionability (e.g., BRCA mutations), special efforts can be made to find people at genetic risk and provide early life-saving interventions. For variants of lower risk or penetrance (e.g., polygenic risk for breast cancer), such variants might

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be used to modify the screening regimen for average persons, for example, by starting screening at an earlier age or more frequently.

WHAT ARE KEY EVIDENCE NEEDS IN USING INCIDENTAL GENOMIC VARIANTS IN SCREENING AND RISK ASSESSMENT?

Evidentiary requirements for population screening have been suggested by the WHO Wilson and Jungner 1968 criteria (Andermann et al., 2008). Over the years, they have been adapted by various groups and applied to numerous topics, including genetic screening and specifically newborn screening. Screening of asymptomatic people in the general population has required significant evidence of a favorable balance between benefits and harms. The main issue in using variant information in opportunistic screening (assuming the application of whole exome or whole genome methods) is how utility is defined for information that is already generated and "in hand." Assuming we can assess both the quality of variant calls and their annotation, we might phrase the underlying question more accurately as, What should be the evidentiary standards for clinical utility for use in disease screening?

Since 2013, the American College of Medical Genetics and Genomics and other groups have attempted to address this issue. The college recommended that when NGS is used clinically in children or adults, 56 genes related to 24 inherited conditions be examined in addition to the intended genetic information from testing (ACMG, 2013; Green et al., 2013). Each of the recommended conditions was chosen on the basis of having a high penetrance and being clinically actionable. Genetic variants from these 56 genes include those either known or predicted to be pathogenic. High penetrance in this case signifies strong clinical validity, and "clinical actionability" implies that clinical benefits will accrue if the patient and provider had the information in hand. In this case, the concepts of screening apply since the patient has not been tested because of clinical signs or symptoms related to these 56 genes.

This list includes a number of genetic conditions for which evidence-based recommendations for testing and counseling have been promulgated by evidence-based groups. For example, the U.S. Preventive Services Task Force has specific recommendations that were updated in 2013 (Moyer, 2014) on counseling and testing women for BRCA mutations if they have a high-risk family history (but discourages the use of BRCA testing in the asymptomatic general population without a high-risk family history). A recent study from Israel, however, suggests that population-wide screening in the Ashkenazi Jewish population may be required to identify a larger proportion of women with BRCA mutations in the absence of family history. Similarly, there are guidelines on testing for Lynch syndrome by the National Comprehensive Cancer Network (Hampel, 2014) for people with a certain family history and by the Evaluation of Genomic Applications in Practice and Prevention Working Group (EGAPP, 2009) for all newly diagnosed cases of colorectal cancer. For other conditions, such as familial hypercholesterolemia, recommendations exist for cascade screening in families of affected patients but not for population-wide screening for genomic variants (Ned Ré and Sijbrands, 2011). For other conditions on the list, perhaps because of the rarity of some of these conditions, no evidence-based recommendations exist, only expert opinions or individual publications. For many conditions, the frequency of mutations and other variants can be much higher than clinical detection and expression, suggesting a need to look at the balance of sensitivity, penetrance, and potential benefits and harms of available interventions. Obviously, the utility of genetic variants

for screening is context dependent (e.g., population, ethnic group, presence of family history, and so forth).

Other groups have attempted to provide evidence-based approaches for the classification of genomics variants by levels of evidence. The knowledge synthesis center sponsored by the Evaluation of Genomic Applications in Practice and Prevention Working Group published a three-stage approach for "binning" incidental genomic variants using evidence-based principles (Goddard et al., 2013). In stage I, incidental findings that do not reach a minimum evidence threshold are ruled out. An interrater agreement is used in the evaluation process as well as comparison to an expert-based approach. Criteria for clinical actionability is documented in stage II so that experts can consistently consider and make recommendations on whether results should be routinely reported (stage III). Such an approach has been piloted on a limited basis and is now being adapted to an ongoing National Human Genome Research Institute–funded project, ClinGen, which seeks to catalogue information on the validity and utility of emerging genomic variants. Economic analysis of returning findings to patients given rapidly dropping costs of sequencing should also be addressed.

WHAT ARE KEY RECOMMENDATIONS FOR COLLECTING EVIDENCE IN ORDER TO USE INCIDENTAL GENOMIC VARIANTS IN OPPORTUNISTIC SCREENING AND RISK ASSESSMENT?

Here we propose for further exploration the following key recommendations pertinent to clinical utility for opportunistic screening. Developing approaches for ensuring the analytic validity and clinical validity of incidental genomic variants and a robust return of result process are essential.

1. Develop and sustain an evidence-based process, by an independent group(s) with full stakeholder engagement and consideration of patient preferences, that would review and continuously update what we know about the balance of benefits and harms of returning incidental genomic variants to inform future screening and risk assessment
2. Conduct follow-up studies on the benefits and harms of returning agreed-on incidental genomic findings to patients who have undergone NGS. Outcome measures would include the efficacy of various communication options, behavioral, medical, and economic outcomes such as patient and provider uptake of medical interventions and screening recommendations, anxiety, and so forth.
3. Explore the need for randomized clinical trials. A key question here is whether randomized clinical trials are required or whether we might rely on other implementation research designs, such as pragmatic trials and well-designed observational studies conducted in defined health care systems and representative populations. As knowledge accumulates, costs decline, and societal demands increase, should we consider alternative approaches to accumulate knowledge on clinical utility in the real world?
4. Explore similarities and differences in evidentiary requirements for returning genomic findings to people who have undergone NGS for medical diagnostic purposes as opposed to population-wide testing using NGS, such as in newborn screening or screening healthy persons at other stages in life. This question will become more and more salient with further proliferation of NGS testing and direct personal genomic testing services. How do

we consider population and ethnic diversity in the likelihood of harboring genetic variation that could be used in risk assessment and disease screening?

REFERENCES

ACMG (American College of Medical Genetics and Genomics). 2013. Incidental findings in clinical genomics: A clarification. *Genetics in Medicine* 15(8):664–666.

Andermann, A., I. Blancquaert, S. Beauchamp, and V. Déry. 2008. Revisiting Wilson and Jungner in the genomic age: A review of screening criteria over the past 40 years. *Bulletin of the World Health Organization* 86(4):241–320.

EGAPP (Evaluation of Genomic Applications in Practice and Prevention Working Group). 2009. Recommendations from the EGAPP working group: Genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. *Genetics in Medicine* 11(1):35–41.

Goddard, K. A., E. P. Whitlock, J. S. Berg, M. S. Williams, E. M. Webber, J. A. Webster, J. S. Lin, K. A. Schrader, D. Campos-Outcalt, K. Offit, H. S. Feigelson, and C. Hollombe. 2013. Description and pilot results from a novel method for evaluating return of incidental findings from next-generation sequencing technologies. *Genetics in Medicine* 15(9):721–728.

Green, R. C., J. S. Berg, W. W. Grody, S. S. Kalia, B. R. Korf, C. L. Martin, A. L. McGuire, R. L. Nussbaum, J. M. O'Daniel, K. E. Ormond, H. L. Rehm, M. S. Watson, M. S. Williams, and L. G. Biesecker. 2013. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genetics in Medicine* 15(7):565–574.

Hampel, H. 2014. NCCN increases the emphasis on genetic/familial high-risk assessment in colorectal cancer. *Journal of the National Comprehensive Cancer Network* 12(5 Supplement):829–831.

Moyer, V. A. 2014. Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine* 160(4):271–281.

Ned Ré, M., and E. J. G. Sijbrands. 2011. Cascade screening for familial hypercholesterolemia (FH). *Public Library of Science Currents* 3:RRN1238. doi:10.1371/currents.RRN1238.

Teutsch, S. M., L. A. Bradley, G. E. Palomaki, J. E. Haddow, M. Piper, N. Calonge, W. D. Dotson, M. P. Douglas, and A. O. Berg. 2009. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: Methods of the EGAPP working group. *Genetics in Medicine* 11(1):3–14.