Return of Anticipated and Incidental Results from Next-Generation Sequencing: Implications for Providers and Patients

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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.

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OVERVIEW

Next-generation sequencing (NGS) technologies, including exome or genome sequencing, are in the early phases of transitioning from research laboratories into the clinical arena. At present, much of this work occurs at major academic medical centers, but it will likely expand to community hospitals and medical clinics. NGS analysis can give not only anticipated results relevant to a clinical diagnosis but also incidental findings that pose additional challenges for the provider and patient. In this paper we explore evidence gaps and requirements for the successful integration of NGS into clinical settings from the standpoints of the patient and provider.

NGS is an emerging component of clinical care ranging from diagnostic to screening applications. On the basis of the information presented at meetings of the IOM Roundtable on Translating Genomic-Based Research for Health over the past year and a half (IOM, 2014), we identify three different clinical scenarios in which NGS is currently being utilized. These cases illustrate information that providers communicate with their patients. First, in oncology, patient tumors are being sequenced to search for clinically actionable mutations. In this context, the information may provide guidance for clinical decisions. Second, for rare Mendelian diseases, NGS can provide an answer to a patient with a previously undiagnosed disease. As such, this may end the diagnostic odyssey that many rare-disease patients experience, particularly those with severe pediatric conditions. However, in many cases the genetic information is not clinically actionable. Third, NGS is also used for diagnosis in the context of common conditions in adult patients, such as heart disease. In these settings, the patients differ significantly, and the medical professionals providing the information will also be different. However, in all three settings, there is the potential for generating incidental findings.

Provider training in genetic analysis and interpretation, as well as patients’ ability to understand and apply what they are told across the breadth of settings, is very diverse. It is

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1 On detail from the National Institute on Alcohol Abuse and Alcoholism.
2 The authors are participants in the activities of the IOM Roundtable on Translating Genomic-Based Research for Health.
unknown if providers need access to clinical genetics experts in developing a clinical plan, or if
the provider would have sufficient guidance from laboratory reports. It is also unknown whether
a provider would know what information is valuable to return or is able to counsel a patient
adequately as to what could be found before the sequencing is performed. In addition, it is
unknown if and how patients want to be informed of the incidental findings and how they would
use additional resources and materials that are patient friendly and developed for specific
populations. Incidental findings may or may not be diagnostic, identifying potential risks of
varying magnitude. It is important for providers to know how to communicate this information
as well as the associated uncertainty. It is equally important for patients to understand the
incidental findings concept and how it differs from a diagnosis, so they can make the best use of
this information to address potential health issues. People receiving NGS results vary in their
ability to understand complex genomic information and in their emotional readiness to hear
results that may or may not answer the clinical question that led to the test. Some will desire only
actionable information, whereas others may be highly curious regarding personal genomic
findings even when there is no apparent clinical utility (Bunnik et al., 2014). Furthermore, some
individuals might take actions (e.g., drastic dietary or lifestyle changes) on the basis of NGS
results because of an incomplete understanding of the limitations of variant interpretation.

EVIDENCE NEEDS TO ADDRESS CHALLENGES IDENTIFIED FOR BOTH
PROVIDERS AND PATIENTS

Clinical utility of anticipated and incidental findings from NGS is limited by the ability to
interpret the functional relevance of individual variants. The interpretation of identified genetic
variants is dependent on data available in the literature, as well as data coming from ongoing
research in individual, pathology, and reference laboratories and big data initiatives. On the basis
of such information, the clinical interpretation of a variant can change rapidly. Also, what
constitutes a clinically actionable finding can also change quickly, as new therapies (e.g., gene
therapy) and new treatment approaches are developed. These considerations raise the question of
how new data regarding the clinical significance of identified variants can be translated and
communicated to providers in a timely manner so that patients can get the most up-to-date
relevant information.

Clinical utility may be limited if the information is not valued and acted on by the patient or
provider. A variant for a disease other than the clinical indication for the test, or a variant with an
uncertain interpretation, may increase cost through further testing. All findings may add to the
patient’s burden of deciding if and how to inform biologic relatives who may or may not want
the information. Optimally, a discussion between the provider and patient would take place prior
to NGS to give the patient and provider the opportunity to decide what information will be
reported.

KEY RECOMMENDATIONS

We propose the following key recommendations to better prepare clinicians to return and
patients to receive NGS results.

1. Providers should discuss the patient’s preference for receiving incidental findings before
data are available; this communication may involve genetic counselors and specialists
and may influence cost.
2. Evidence is needed to identify how individualized communication and shared decisions regarding NGS results fit provider and patient needs.
3. Databases that house the most current research findings and their associations with diseases/conditions must be updated and maintained, and methods to assure timely transmission of data to providers are needed.
4. Effective clinician education is needed on the use of clinical decision supports for implementing anticipated and incidental NGS results.
5. Best practices from experiences at academic medical centers should be identified to facilitate expansion of NGS to clinical practice at other health care provider settings.

REFERENCES
