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Next Generation Sequencing in the Clinic: Are we Ready?

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Leslie G. Biesecker

1) Are clinical genomic data different from other medical test data? Should they therefore be handled differently?

Genomic test data (clinical genomes and exomes) are stupendously complex, but so are a number of other complex medical tests. So, genomics is not different solely because of this complexity. But this similarity to other tests obscures two important aspects of genomic data that require that a nuanced response to the second question is given. The first is that there are a few genes in a genome or exome that are known counseling land mines (e.g., Huntington disease and frontotemporal dementia ¹). It is an open question as to how we should deal with these genes in the context of genome and exome sequencing. Problems associated with testing these genes can be avoided by ensuring that the professionals who order, perform, analyze and interpret these genomes and exomes are trained and cognizant of the challenges that such testing entails and manage the testing appropriately. Stumbling on these is inexcusable - these land mines are known and they should be anticipated. The second unique aspect of a genome or an exome test is the breadth of the testing. Even in this aspect, genomics is not truly unique. Ironically, the general physical examination comes closest to a genome or exome in the breadth of what is being sought, what might arise “incidentally” and the fact that it is difficult to consent a patient to the potential consequences of this evaluation. The irony is that it is the oldest test and we are all quite comfortable with it. However, human beings, especially ones who are ill, are complex emotional creatures and are poorly equipped to absorb information regarding potential health threats on anything near the scale of a genome. At the same time, it is possible to extract a clinically useful subset of the data and use that to modify the health care of a patient ^{2, 3}.

My conclusion is that clinical genomic data are the same as other complex medical data and need to be interpreted and delivered to the patient by professionals (typically a molecular geneticist, clinical geneticist, and genetic counselors) who have the skills to interpret these results in the context of the test methodology, the theoretical background of genetics, Bayesian reasoning, and a myriad of other factors.

2) On what grounds should findings from genetic tests be returned to patients and who should decide this? Should we offer patients the choice as to whether to sequence certain disease causing genes?

These are the core challenges that we face - what subset of the information should be returned and how to decide what subset this should comprise. It is a given that the patient will need to participate in this decision, but it is also clear that patients don't have the knowledge and tools they need to make these decisions. I have performed a number of the informed consents for the ClinSeq™ study⁴ and when I tell participants that one of the goals of ClinSeq™ is to learn what subset of the data they want back, the typical response is "but I want it all". This enthusiasm and optimism is wonderful but no human being can possibly absorb or use 6 GB of genomic sequence, or even 60 MB of exomic sequence. My clinical experience is that a typical patient is information saturated within 20–40 minutes of discussing a single test result. We have returned unexpected cancer susceptibility mutations (just one variant per person) to ClinSeq™ participants and the only way to summarize the response is to say that they are confused and overwhelmed. These kinds of results can be extracted from the data, they can be returned, and they can be used to alter the management of the patient, but it is emotionally challenging for the patients and needs to be performed thoughtfully.

Clinical genomic data must therefore be stratified and prioritized to bring to the fore the most relevant and useful data for the individual patient and deliver it to them in a way that allows them to absorb and use the result. It just is not true that all genetic testing is as laden as is a result for Huntington disease. Much of it is actually pretty mundane for most patients and could be delivered in creative ways such as through the internet or computer-based media, reserving the critical results for in-person genetics professional delivery. We therefore need to develop an empirical research base upon which to determine which results can be returned by which modes for which patients.

3) What infrastructure – practical, regulatory, educational and medical – needs to be developed if clinical sequencing is to best serve patients' needs?

We have essentially none of this in place and the needs are overwhelming. Building all of these resources simultaneously for the predicted broad uses of sequencing in the clinic is impossible -we cannot justify the cost because we have not yet demonstrated the utility and we can't demonstrate the utility until we have the infrastructure. One approach would be to start where it would be easiest to use the technology today and where it is most likely to be successful. Currently, this is in the realm of uncharacterized (typically rare) diseases that have eluded the so-called Casablanca diagnostic strategy ('round up the usual suspects'). Such patients are small in number but currently consume large amounts of diagnostic resources in a long (sometimes lifelong) search for a diagnosis. If the disorder is likely to have a Mendelian genetic basis, whole genome or exome sequencing can end this diagnostic odyssey. If this is where the testing is most likely to be useful today, then we can gradually build a regulatory framework, clinical expertise and training, informatics, and legal construct to support that testing and expand it to more common disorders. We can build the infrastructure to interpret secondary variants, pharmacogenetics, newborn screening, etc. This 'glass half full' approach exploits the things we know how to do best, instead of focusing on the 'glass half empty' approach which focuses on the limitations of our data, fears of ethical calamities, and plain old fashioned human fear of change.

4) Will sequencing-based diagnostics become routine and fulfill patients' expectations and what is the most crucial single challenge now?

Among the reactions we have struggled in returning results in ClinSeq™ is not those of the participants, but rather that of some of their physicians. In more than a few cases, the

physicians have been dismissive or even angry with us for finding, for example, a mutation that predisposes to cancer in a patient with no personal or family medical history. Our surprise at this reaction emanates from an underappreciated collision of values, priorities, and incentives. We feel that a success in ClinSeq™ is to identify persons who have an increased liability toward illness before that illness manifests in them or their immediate family. Yet, what we are learning is that the busy primary care physician is having a hard time fitting this into their practice paradigm and they are going to need a lot of support, guidance, and (to be honest) remuneration, to convince them to do this work. This experience has taught us that one of the greatest challenges we geneticists face is to convince our colleagues of the value and utility of a genetic model of preventive medicine, but more importantly, to provide the support and tools to make this approach to medicine a routine part of the health care landscape.

Wylie Burke

1) Are clinical genomic data different from other medical test data? Should they therefore be handled differently?

Clinical genomic data have the same purpose as other medical tests: to provide information to improve a patient's health care. In that sense, they are no different from other tests. However, clinical genomic data raises challenges that - while not unique - are different in scope^{5, 6}. These challenges include: (1) a high likelihood of incidental findings; (2) information relevant to family members; and (3) findings which by current standards of practice call for pre-test counseling, to ensure that the patient understands the nature of the information to be provided by testing, and has the opportunity to decline testing. This latter category includes information about carrier status⁷ and about future health risks for which there is no treatment⁸. There is an urgent need for consensus development on the appropriate handling of each of these issues. We can anticipate, however, that practice standards for genomic data will incorporate lessons derived from the history of genetic testing⁹: privacy of health records should be assiduously protected; patients should receive sufficient information before testing to make an informed decision to proceed; and both counseling and educational tools should be developed to assist patients to understand test results, including both personal and family implications.

2) On what grounds should findings from genetic tests be returned to patients and who should decide this? Should we offer patients the choice as to whether to sequence certain disease causing genes?

If a genetic finding is generated as a result of clinical testing, practice standards and consensus-based guidelines should determine what results are returned. However, these standards and guidelines do not yet exist – and there is an urgent need to develop them. They should incorporate patient views, and respect patient choice, but must also take into account appropriate use of clinical resources, including laboratory time and resources involved in generating clinical findings from raw sequence data and clinician time spent in pre- and post-test counseling⁵. As with other medical resources, patients should not have an unlimited opportunity to request genomic testing results¹⁰. Most health insurers currently define eligibility criteria for BRCA testing; we are likely to see similar criteria developed in the future to define appropriate clinical use of sequencing tests, including the appropriate range of incidental findings to return.

3) What infrastructure - practical, regulatory, educational and medical - needs to be developed if clinical sequencing is to best serve patients' needs?

We need reliable databases to assist laboratories and clinicians to interpret the clinical significance of sequencing-based data – and by extension, we urgently need the research to

populate those databases⁵. Both clinicians and patients will need tools to assist them to interpret test results. Some of this work can be done based on our current limited understanding of genomics. For example, pharmacogenomic data offer an opportunity to develop point of service guides for clinicians and educational tools for patients¹⁰. Ultimately, however, the needed infrastructure requires more comprehensive data than we have. Without better information about the clinical implications, clinical sequencing is largely a promissory note.

4) Will sequencing-based tests become routine and fulfill patients' expectations and what is the most crucial single challenge now?

Sequencing tests will undoubtedly find a place in clinical care. However, the scope of clinical use is hard to predict at this time. Sequencing-based tests may be used primarily to address specific questions in certain specialties – eg, sequencing of a tumor genome to direct care; or use of whole genome sequencing to evaluate multigenic disorders or work up an undiagnosed individual with a rare phenotype - or may achieve more widespread clinical use. The reason for this uncertainty relates to the most crucial single challenge: lack of sufficient understanding of the phenotypic implications of sequencing-based data. We need much more research to understand the clinical implications of such data – and by extension to understand when and how such data can help to improve health care.

Whether sequencing-based tests will fulfill patients' expectations therefore depends on what those expectations are. Genomic information is likely to improve health care in a variety of ways, but is unlikely to serve as a universal guide to preventing disease – because genetic risk is only one contributor among many to the common conditions that make up most of the disease burden in our society¹¹. In the genomic era, we will still need to exercise, eat prudently, and avoid cigarettes.

Isaac S. Kohane

1) Are clinical genomic data different from other medical test data? Should they therefore be handled differently?

Genomic tests are, with one notable exception, qualitatively no different than any other clinical test whether it be electrolyte monitoring, complete blood cell count or cranial magnetic resonant imaging. Genomic tests, like all other clinical tests, provide a probabilistic measure of certainty that a specific pathophysiological state is present (i.e. diagnosis) or will be present (i.e., a prognosis). Whether genomic or conventional, all these tests are used for clinical decision making whether in the context of screening asymptomatic individuals or managing individuals with a complaint. The costs of each the aforementioned tests including whole genome sequencing, are typically less than a couple of thousand dollars and the volume of data generated is typically not more than a few terabytes. However, the most important difference between genomic tests and clinical tests is that the medical establishment and the medical industrial infrastructure believe them to be very different. This perception is due to a number of well documented deficiencies in medical education regarding genomic tests¹², discomfort on the part of clinicians in interpreting the genomic tests^{13, 14}, and the complete lack of infrastructural support in current electronic medical records for the acquisition of and processing of genomic and genealogical data¹⁵. The consequence of these deficiencies has been a remarkable willingness to consider forms of automated decision support and knowledge creation that are at best grudgingly accepted for other kinds of testing mostly because clinicians believe they can use intuition and experience to determine the right time to order conventional clinical tests and are unaware of cognitive biases such as those caused by insensitivity to the prior probability of diseases¹⁶. Most clinicians are under no such delusion with regard to genetic testing and

therefore although the differences are qualitatively minor, the application of principles of rational decision making (e.g., maximizing expected utility¹⁷) are more likely to be applied to genetic tests than to existing clinical tests.

The one area in which genetic tests are qualitatively different is that even a small fraction of an individual's whole genome¹⁸ is highly identifying. This makes the stakes of data security and privacy policies much higher. Genomic data cannot be shared with other researchers without a much higher likelihood of disclosure of identity than with other data types. The risk of disclosure is growing significantly with the accumulation of independent non-medical DNA databases such as those maintained by the system of criminal justice in the US.

2. On what grounds should findings from genetic tests be returned to patients and who should decide this? Should we offer patients the choice as to whether to sequence certain disease causing genes?

The genomic data of a patient should be immediately available to the patient just as all clinical measurements increasingly are. However, under the principles of the Hippocratic corpus¹² “first, do no harm” the interpretation of these data by clinicians should be limited to that subset for which there is a substantive evidentiary base and a quantifiable measure of certainty. In the absence of such a clinical filter on these findings, there will be an overwhelming return of false, misleading and potentially harmful findings leading to unneeded additional tests and treatments that will make the unnecessary morbidity and costs induced by the prostate specific antigen screening seem paltry in comparison¹⁹. In this context, in asymptomatic patients the prognostic value for most disease is relatively slight as demonstrated by the recent paper of Roberts et al.²⁰. Conversely, when there is a clinical indication, the increased prior probability of a pathogenic variant being present substantially decreases the likelihood of false positives and boosts the positive predictive value of testing genes implicated in diseases that might be responsible for the clinical characteristics the patient is manifesting.

3) What infrastructure – practical, regulatory, educational and medical – needs to be developed if clinical sequencing is to best serve patients' needs?

The missing infrastructure for genetic tests falls into two categories: The technical infrastructure such as data representation, storage, and incorporation into electronic medical records will require concerted effort but is conceptually straightforward to implement²¹. Less obvious is the regulatory surround, specifically as pertains to the identifying nature of genomic data and how this might affect what are the current flows of patient data either for reimbursement, care or research. Most problematic is the broad lack of education in genomic science throughout our clinical establishments, medical schools and training programs²². Without this knowledge base and skill set, which includes a well grounded familiarity with probabilistic reasoning, physicians will not be able to serve as authoritative decision makers for clinical genomics. The recent emergence of a half dozen whole genome diagnostic companies suggests that a future infrastructure may in fact be a hybrid of genome-specific interpretive software intercalated into the conventional systems used in provider practices. That is, in most practices, the authoritativeness on genomic science will derive from the up-to-date knowledge base and software rather than local expertise. Moreover it is highly likely that that infrastructure will include a patient-based component, so that patients can obtain authoritative advice even when the medical establishment is silent.

4) Will sequencing-based tests become routine and fulfill patients' expectations and what is the most crucial single challenge now?

There is little doubt that sequence-based tests will be routine used and indeed cheaper than many other high technology tests. Although patients' expectations regarding the oracular capabilities of genomic testing, set by over a decade of public, grandiose and occasionally portentous forecasts, are unlikely to be met in the context of asymptomatic, healthy patients, they will be exceeded in the individualization of therapy and the recasting of poorly defined disease within a framework of precision medicine²³. In order to realize this, we have to ensure that, whether it is in the commercial domain or in the public domain, we obtain the most authoritative and up-to-date, continually revised knowledge-base as to the clinical meaning of genomic variants. Further, either the medical establishment will rise up to the challenge of the incorporation of this knowledge-base into daily practice or alternative channels for the authoritative application of genomic knowledge will develop and grow.

Sharon E. Plon

1) Are clinical genomic data different from other medical test data? Should they therefore be handled differently?

Over the last 20 years, my graduating class from medical genetics fellowship has frequently argued the "What's so special about genetic testing?" question. Technically, genetic tests are handled like other medical tests including being ordered by a physician, based on a medical problem (including family history) and resulted back to a physician for interpretation to the patient. In my experience there are several major differences from other tests. First, is the ability of genetic tests to be predictive literally decades in advance of disease such that there is a potential likelihood of an adult onset disorder being identified in a child. Cholesterol levels are predictive of heart disease but this is categorically different from the near certainty of developing Huntington chorea if a trinucleotide amplification of greater than 39 repeats is identified²⁴. Genome-scale tests also make the likelihood of incidental findings much greater than targeted genetic tests²⁵ and potentially more than other diagnostic modalities such as an MRI.

The other unique aspect is the interrelationship of genetic test results among family members. The child with a mutation for an adult onset disorder identified in a genome-scale test likely inherited it from a parent now also at risk for this disease. Importantly, for single gene or limited panels of genes it is often recommended to first test a member of the family with disease in order to identify the causative mutation in the family before testing at-risk individuals. However, these individuals may have two different physicians and unfortunately, be cared for in two different medical systems. Medical records and insurance companies are not currently able to support family-based genetic analysis. For example, guidelines for *BRCA1/2* genetic evaluation recommend that testing initiate with a member of the family with cancer, e.g., a woman with end-stage ovarian cancer - not for her own health – but to provide critical information for her daughters [<http://www.cancer.gov/cancertopics/pdq/genetics/risk-assessment-and-counseling/HealthProfessional>]²⁶. However, the physician ordering the test is often required to document medical necessity to obtain insurance coverage of the genetic test for the patient being tested. Similarly, the daughter's insurance company doesn't see the reason to fund testing of the mother. A more rational system to handle family-based testing would make genetic analysis much more efficient and cost-effective²⁷.

2) On what grounds should findings from genetic tests be returned to patients and who should decide this? Should we offer patients the choice as to whether to sequence certain disease causing genes?

Results from genetic testing have been routinely provided to patients since the advent of clinical cytogenetics in the 1960's extending to DNA-based linkage in the 1980's and sequence-based tests in the 1990's. Genome-scale molecular tests are the next phase of this realm of medical technology. Whole exome tests are now being offered and will clearly improve diagnosis of patients/families with a wide variety of phenotypes^{28–30}. The medical genetics and genetic counseling professions were designed to facilitate appropriate and professional provision of genetic information to patients. Although these professions are small we should not be in a rush to obviate the use of such professionals for genome-scale testing as there are many challenges ahead and the possibility of mis-interpretation is amplified as the scale of testing increases. In contrast, pharmacogenetic loci may have more clear-cut medical benefit with less controversy or need for specially trained practitioners for disclosure of the data.

There are several efforts underway to generate a consensus list of medically actionable genes that should “always” be reported³¹. However, as many of us work to create such lists they are long – many variants imply actionability if you know enough about them and conversely many databases currently incorrectly annotate variants as disease causative making fully automated reporting of incidental findings difficult³¹. In my opinion comprehensive genome-scale reports which include medically actionable variants and/or carrier status should only be provided if the laboratory is provided clear documentation (consent signed by patient and ordering physician or genetic counselor) that the patient understands these possible result types. One will do less potential harm by not providing information that isn't going to be adequately interpreted or transmitted. For example, in the case of cancer genomes the germline genome is being sequenced as a control that is subtracted away before reporting cancer-specific mutations. If labs make clear the specific cancer genome test being provided there is no reason to compel them to report actionable germline variants. Performing analysis of the germline data adds costs to the cancer test including involving lab directors with the appropriate germline expertise to avoid inaccurate reports. Research on how often cancer patients (or parents of childhood cancer patients) want this additional germline data interpretation is underway [<http://www.genome.gov/27546194#a1-2>].

3) What infrastructure – practical, regulatory, educational and medical – needs to be developed if clinical sequencing is to best serve patients' needs?

With the introduction of any new genomic technology there is a period where laboratories all set their own standards and then consensus guidelines are generated. Clearly guidelines are needed for next generation test methodologies with regard to the quality of the data needed to call variants, calling algorithms and reporting methodologies. The educational need of the medical professionals receiving the reports is proportional to the comprehensiveness of the reporting. If labs endeavor to provide reports containing potentially hundreds/thousands of novel or rare variants identified in a clinical exome this then necessitates creation of genomicists (physicians able to analyze these results) to receive them in order to avoid physicians overcalling rare variants as causative of disease. Experience from *BRCA1/2* testing where hundreds of thousands of women have been tested has demonstrated the significant amount of data needed to appropriately interpret each new variant²². This emphasizes the need for appropriately curated variant databases and warns against physicians assuming that every rare or novel variant in a disease associated gene is disease causing³². The educational burden becomes much greater as we try to combine data types or incorporate low to moderate risk alleles into clinical medicine. We also need to be

clear to the public that we are just at the beginning of genome-scale clinical testing; the current tests aren't the ultimate test. For example, analysis of the microbiome or sequencing of specific cell types will come online as technology and bioinformatics improves.

4) Will sequencing-based tests become routine and fulfill patients' expectations and what is the most crucial single challenge now?

Genome-scale sequencing tests will rapidly become routine for the diagnosis of children and adults with major medical problems for which there are a very large number of possible Mendelian or high penetrance genes. The current costs of disease panels, e.g., panels of anywhere from 5–50 potentially causative genes are similar to whole exome tests. Thus, whole exome (and subsequently whole genome tests) are rapidly becoming more efficient. They will likely become the frontline test for Mendelian or high penetrance disease-associated mutations. This transition will accelerate as turnaround times shorten and technology improves for assessing sequence, copy number and rearrangements within the same test. Similar improvements are crucial for cancer exomes/genomes becoming frontline tests.

There is however, a very large gap between reporting results for single gene disorders and understanding how to combine data in a clinically meaningful way for the much larger number of genetic changes that individually have mild-to-modest impact on disease risk such as in diabetes. Algorithms to combine gene-by-gene interactions (multiplied many times over) for common variants are far from clinical application and also require the addition of environmental exposures in making disease prediction. An example of this type of work is a very recent study which combined genotyping of 32 common polymorphisms with measurement of sugar-sweetened beverage consumption on obesity outcomes³³. These types of combinatorial tools are clearly needed for genome scale testing to be used as routinely as a cholesterol level is today for prediction of common diseases such as atherosclerosis.

Ron Zimmern

1) Are clinical genomic data different from other medical test data? Should they therefore be handled differently?

Medical test data may be of different types. Not all are, or should be, handled in a similar manner. Clinical genomic data can be considered to derive from what I call 'open ended tests'. Such tests include the karyotype, X-rays and other imaging modalities, and also the clinical examination. They are 'open ended' because the test may reveal more than the investigator seeks or desires to know. A karyotype may be performed to determine the presence or absence of a trisomy; but may show an unexpected translocation. Thoracic imaging may be carried out to look for emphysema; but may show an unexpected cancer.

'Open ended' tests have always posed a problem to the physician. They show up unexpected or unwanted data that will need interpretation. Clinical judgment as to how best to proceed will be essential. My personal belief is that the problems posed by clinical genomic data are conceptually the same as those posed by any other 'open ended' test. I am unimpressed with the argument that because they are likely to reveal information to other family members this poses a new ethical problem. All tests will do this to some extent. The diagnosis of cancer in a person doubles the risk in a first degree relative³⁴. If there are ethical issues, they lie in how the patient ought to handle the information rather than that the patient should or should not undertake the test in the first place.

'Open ended' tests differ from 'closed' tests such as uric acid or sodium measurements. Genomic assays may be set up in such a way as to mimic a 'closed' test, such as when

specific assays are designed to assay and interrogate variants relating to a particular problem.

2) On what grounds should findings from genetic tests be returned to patients and who should decide this? Should we offer patients the choice as to whether to sequence certain disease causing genes?

My default is to suggest that it is the patient who should decide. But that default position needs to be qualified. The patient seeks an opinion about a specific clinical problem. Technology will allow the investigation of the entire genome ('open ended') to be converted to a conventional, 'closed', test that only looks for variants relevant to that problem. I believe that, at present, with perhaps exceptions for very difficult complex problems (where 'experimental' diagnostic techniques using the entire genome might be used) genomic data should be implemented in the clinical setting as specific arrays directed at specific situations. Interpreting such arrays is time consuming and complex enough. Our logistical, bioinformatic and human resources (and our knowledge) are limited; these barriers speak against the routine use of the whole genome at present.

But, assuming a full genome sequence, the issue of what should be returned to the patient should be a matter for discussion between physician and patient. Some will only want information relevant to the clinical problem at hand. Others will want information related to other unrelated but clinically treatable or preventable conditions; while some will want information about such conditions even if not treatable or preventable. The patient's view should be taken into account but the view of the physician is also important. Clinical judgment must form an important component of the decision making process. Explicitness and transparency are key, which must take into account logistics, interpretation, and other resource considerations.

The clinical examination will sometimes reveal a problem totally unrelated to that for which the patient sought help. It is normal practice, and entirely ethical, that the physician draws the patient's attention to the new problem and investigates appropriately. Variants, even if significant, are in one sense like this, but in another sense not. The unexpected pathogenic variant, unlike the unexpected clinical finding, is indicative not of disease but the risk of disease. How might that change the approach?

3) What infrastructure – practical, regulatory, educational and medical – needs to be developed if clinical sequencing is to best serve patients' needs?

The organization of clinical services and of laboratory provision, the training of specialists in genomic pathology, genomic medicine and bioinformatics, the education of physicians and other clinical staff, will all be needed to prepare for the advent of genomic medicine³⁵. Its excitement and potential will need to be balanced against unwarranted hype. The difficulties of interpretation should not be underestimated. The complexities of human biology and the place of epigenetic mechanisms, of the dynamics of gene transcription and translation, and of post translational changes, for example, must all be recognized; and this before considering the influence of the microbiome. The primacy of the genomic sequence is clear, but citizen and physician alike must understand that sequence information will be only one of many determinants of disease, and that too great an emphasis should not be placed on it, except when dealing with highly penetrant inherited or heritable disorders. Biology is complex; interpretation equally so.

But education aside, the other essential infrastructure will be bioinformatic. Putting all these data together and making sense of them will require a step change in bioinformatic resources and understanding. Without bioinformatics, there can be no practical ways of interpreting

the genome for clinical benefit. I would wish to see the establishment of a new specialty, that of the clinical bioinformatician, sitting at the interface between the genomic pathologist and physician on the one side and the academic and mathematical bioinformatician on the other. This will require the establishment of a professional accreditation body and appropriate codes of practice³⁵. Regulation is of course important, but I am essentially against genetic exceptionalism. All personal medical data should be regulated, but I see no coherent or convincing argument that genomic data should be regulated any differently to any other medical data.

4) Will sequencing tests become routine and fulfill patients' expectations and what is the most crucial single challenge now?

I hope that certain forms of sequencing tests will become routine. But in this early stage of clinical development, I would suggest that these be confined to specific sequences directed at specific clinical problems, be they developmental delay in childhood, cancers or sets of single gene disorders. Genome based diagnosis will have the potential to save resources by preventing the need to undergo phenotypic based tests which more often than not will not lead to a definitive diagnosis. The expectations of the citizen must be reduced for the present, but not at the expense of understanding the future potential of this technology. This is a difficult message to market and poses a critical challenge.

For general readings recommended by Dr. Zimmern, see^{36–40}.

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