Published in final edited form as:
Genet Med. 2013 September ; 15(9): 684–690. doi:10.1038/gim.2013.35.

Self-guided management of exome and whole genome sequencing results: changing the results return model

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Return of ES/WGS results is inevitable and ethically appropriate

Exome sequencing and whole genome sequencing (ES/WGS) have become important tools for identifying alleles underlying both Mendelian and complex health-related traits.[1–6] The number of individuals who have undergone ES/WGS has steadily increased, and this trend is accelerating with the rapid commercial adaptation of sequencing-for-service that has made ES/WGS available to nearly any researcher/clinician. In contrast to targeted approaches, ES/WGS simultaneously reveals virtually every allele that might confer risk or benefit to an individual's health and wellbeing. Thus, in essentially every person, ES/WGS identifies alleles that are, or could be, of clinical utility—everyone is genetically "at risk." Accordingly, the scope of individual health-related information generated by ES/WGS is unprecedented[7–10] and challenges many of the existing guidelines, policies and professional norms about returning results from human genetic testing.[11–13]

Bioethics research, albeit limited, and policy recommendations on return of individual ES/WGS (iES/WGS) results to date have focused mainly on issues such as what results should be returned in a clinical setting,[14–16] whether results should be returned at all in a research setting and if so which results,[17–27] and what to do about incidental findings in either setting.[8,27–36] The spectrum of opinions that has emerged about these issues is broad with fairly polarized extremes. Some researchers have argued aggressively that only under few circumstances should research iES/WGS results be returned[12,37–39] and in clinical settings, a filter should be imposed on iES/WGS results so as to force return of results into the existing return of results model.[28] In contrast, others have suggested, often with attribution to the policies of direct-to-consumer genetic testing companies, that all iES/WGS results should be made available to persons who are sequenced.[17] While such normative research on these issues is of intrinsic value, it is likely to be of limited heuristic value now

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that ES/WGS is cheap, fast, and convenient; broadly accessible to researchers, primary care providers and the public alike;[40] and being applied in an increasing range of applications (e.g., non-invasive fetal genetic diagnosis and diagnostic evaluation, genomic research).[40–42] In other words, clinicians and researchers who elect to return results alike are facing right now the practical issue of how to return iES/WGS results.

Most discussions about the ethics of return of iES/WGS results have been framed around a traditional model of clinical genetic testing in which results are discrete dichotomous variables, and return of results is conducted at a fixed point in time when a result(s) becomes available. The meaning of the result (i.e., the scientific and medical understanding of a variant) is also fixed at the point in time when the test/analysis was completed, and the scope of data is constrained to what was ordered, whether it is a karyotype, genotyping panel, or targeted sequencing of one or several genes. The “gate keeper” in this framework is the clinician who decides what test(s) to recommend, presents risks and benefits of the test to the patient, and filters and interprets the result(s).

We suggest that thinking about return of iES/WGS results needs to be reframed in a manner that shifts away from use of this traditional perspective of a fixed, constrained, transactional model based on the ordering of a test for a discrete clinical or analogous research purpose (Supplementary Table S1). Instead, iES/WGS results should be viewed as a dynamic, sustained resource of information that is available to an individual not only at a single point in time, but over many years and even possibly a lifetime.[10,43] If the genome is viewed as a resource (whether the sequencing occurs once or more likely is updated as technology and costs allow), we argue it is ethically appropriate and more practical to change our perspective from “return of results” to one of “managing results.” Even by itself, the phrase “return of results” connotes disclosure of genetic results and reminds us of ethical, legal and professional requirements that regulate disclosure in an instance in which the main agent or actor is the researcher or clinician.[44] In contrast, we share a growing recognition of the value of patient-centric approaches (i.e., shared decision-making) to accessing genetic information[36,45–50] and think that use of the term, “self-guided management of results,” recognizes the agency and autonomy of patients, and the on-going process of receiving and translating results over time.

A self-guided management approach allows individuals to determine whether and when they receive results, in a personalized and time-sensitive context that is responsive to their value system and their perception of possible benefits and risks at a given time point. In this way, individuals can maximize potential benefits of genomic information (beneficence), minimize potential harms (non-maleficence) and preserve their own right to an open future as much or as little as they desire and/or think is appropriate. Much has been written about possible harms of learning certain information about one’s genome, particularly information that suggests poor clinical outcomes for which little preventive or therapeutic action can be taken.[51–53] Empirical evidence that such harms are ever realized, much less on a scale that places large numbers of individuals at risk, is largely lacking and there is a small, but growing body of data suggesting that some adverse responses are attenuated over time or of less concern to individuals as predicted.[54–61] Moreover, it is unclear what is the principle that justifies encouraging strong genetic protectionism. Indeed, the potential for iatrogenic

harms as health care providers learn to respond to ambiguous genetic results (e.g. variants of uncertain significance) is not yet well understood and is perhaps a more critical point of intervention to avoid medical harms.

Self-guided management of iES/WGS results also places the decision to access the information squarely in the hands of individuals (Supplementary Table S1), allowing them to maintain autonomy over how iES/WGS results are used and with whom iES/WGS results are shared, including a range of possible health care specialists (e.g., obstetrician, pediatrician, oncologists, etc.) as needed. Accordingly, individuals can protect the privacy of the information and minimize potential misuse and/or discrimination by others. Under this model, health care providers (e.g., physicians, genetic counselors, etc.) will play lesser roles as gatekeepers and educators, but even more important roles in the translation and interpretation of iES/WGS results. For example, most individuals will likely continue to engage providers about what information is most useful for screening and preventive care at different time points in their life, how the information might impact their healthcare, preventive screening (mammograms, prostate exams), and treatment options; their families and their view of themselves. However, self-guided management of iES/WGS will also reduce the practical burden of forcing providers to act as gatekeepers of the broad scope of results with ever-changing implications for the health of their patients. Health care professionals would still have the opportunity, and even be encouraged, to recommend that a person interrogate their ES/WGS results for potentially relevant information in response to symptoms, attaining a certain age, or having a certain family history.

We contend that an approach to managing iES/WGS results that preserves the right of individuals to full disclosure of and access to meaningful genetic information, according to their own preferences, is the most effective way to respect the four main principles of bioethics (Supplementary Table S2). It would respect individual autonomy about genetic information; maximize the potential benefits of genetic information, both clinical and personal, over time; and minimize the potential harms of either unwanted genetic information, or the harms of not receiving important genetic information. Furthermore, it could increase access to genetic information across populations, and allow for flexibility in how different cultural groups think about results and decision-making about results, thereby respecting the principle of justice. To this end, we think new emphasis needs to be directed toward: (1) developing flexible and contextual approaches for individuals to manage their iES/WGS results; (2) learning about individuals' preferences for results return and how these preferences change over time/circumstances; (3) studying the clinical, psychological, and health-related risks/benefits of results return; (4) articulating what it will mean for individuals to have access to their genome as a resource from birth (if not before) to the end of life; and (5) understanding how health care providers view, incorporate and work within a system for self-guided management of iES/WGS results. Indeed, we think that instead of concentrating on whether to return iES/WGS results, researchers should focus on how, by what mechanisms, to what extent, in what contexts, and with what outcomes, results will be offered and returned.

Challenges to managing iES/WGS results

Existing guidelines and practices for returning genetic results have not adequately anticipated the challenges of managing iES/WGS results. The lack of availability of a conceptual framework, much less a practical approach, for managing ES/WGS results is likely to limit the widespread adoption of full iES/WGS results return. Learning about a specific genetic result is daunting for many individuals; this may seem an insurmountable barrier to making decisions about managing iES/WGS results. Potential recipients may find it difficult to imagine the impact of receiving genetic results on their lives, especially unanticipated results, and therefore the potential for clinical or personal utility may remain largely inconceivable. Even if a recipient is well prepared to make decisions about what results he or she wants, a further challenge is identifying a system of categories or criteria from which the recipient may choose results. Any single system of results classification is not likely to meet the needs of all individuals but yet some system is needed to avoid overwhelming recipients with a near infinite regress of possible ways to classify results.

Among those advocating for offering iES/WGS results for return, many are developing recommendations that streamline decisions about which results to offer by binning iES/WGS results into categories with differing obligations for return. The category into which a result is binned is based on criteria such as clinical utility, clinical actionability, disease severity, and prevalence.[15,16,22] Distinctions among categories are based, at least in part, on the premise that there is an ethical obligation to offer for return some minimum amount of information about certain results (e.g., incidental results that are of high clinical utility).[15,19,23] This seems a reasonable approach for the immediate future using the traditional model of results return. However, it is not clear what the meaning of these categories is in a model in which the iES/WGS results are viewed instead as a resource of information that can be accessed repeatedly over time and motivated by myriad different testing situations. For example, the meaning of a risk variant for cystic fibrosis or a breast cancer varies between an elderly vs. teenage woman. In this context, the nature of obligations shifts away from the urgent and actionable at a fixed point in time, to the need to provide meaningful ongoing access to up-to-date information about iES/WGS results according to the preferences and needs of the individual.

The heuristic value of the categorization of iES/WGS results has not been tested systematically in either a research or clinical setting. Such testing will be important as individuals may not distinguish between results that are clinically actionable versus those that may be diagnostic, explanatory or have benefits other than directly influencing clinical decision making about disease screening, prevention or treatment. Furthermore, efforts to identify categories of iES/WGS results for return have focused almost exclusively on developing expert consensus[14,62] and have not yet given due consideration to participant or patient perspectives on the potential benefits and harms of different kinds of results. Expert opinion is critically important, especially in determining what results have sufficient validity to be made available for return. However, engaging individuals directly about their preferences for receiving results sets the stage for increasing the potential value of genetic information by enabling them to realize opportunities for clinical and personal utility throughout the course their life.

A major challenge of using ES/WGS for diagnosis and predictive risk profiling will be making decisions about the meaning of variants of unknown significance (VUS). However, even among meaningful results offered for return, it will be necessary to determine both what findings people do or do not want to receive and how to effectively communicate risk and meaning. While it may be difficult to ascertain recipient preferences (Supplementary Table S2), individuals may find it challenging to make decisions about which results to receive.[44] This may be due to a general lack of awareness about the role of genetics in health conditions, especially as compared to environmental determinants, further coupled with unrealistic expectations about genetic information. Indeed, most members of the general public have not considered the possibility of receiving iES/WGS results beyond the portrayals in both fictional (e.g., the film GATTACCA) and non-fictional (e.g., the documentary "Cracking Your Genetic Code") mass media.[63,64]

The subjective meaning of results will change for individuals as they age and encounter different environmental exposures over the course of life.[43,46] As new results are discovered and the meaning of established results change (e.g., new evidence about the clinical utility of variants),[10,15] clinicians/researchers will need the flexibility to communicate with patients/participants about these changes. As a consequence, the timing of analysis and interpretation of results will involve more dynamic interactions between clinician/researchers and patients/participants than has been the norm for previous forms of results return.

If standard approaches to disclosure are used, the return of iES/WGS results is likely to require an inordinate amount of time and resources;[10,16,39,42,65] a commitment that cannot be sustained by the current labor force of medical geneticists and or genetic counselors. As more persons seek to manage and receive iES/WGS results, standard approaches to one-on-one counseling will likely prove to be impractical for those both returning and receiving results. Moreover, the large number of results of potential clinical utility will likely surpass the expertise of even the most experienced providers and the "clinical significance" associated with variants identified by ES/WGS will change frequently. Both of these factors would lead to the need for repeated consultations with a researcher/clinician/genetic counselor. Similar to the expansion of newborn screening with tandem mass spectrometry, the most significant expense of ES/WGS will not be the test but in the disclosure of results and follow up. Studying and reformulating standard approaches are likely to fall short given the scope of returnable results and individuals' desires to receive results.[17,47,66]

Additional challenges that will need to be met but for which there are tractable solutions include the need for scalability to accommodate a large number of results (including the increasing number of clinically actionable results and those that could be functionally deleterious) in an increasing number of people and the expected change in annotation and clinical interpretation of variants over time.

A new model for managing iES/WGS results

A system for returning results must be flexible and dynamic to accommodate an ever-changing base of genetic knowledge and the potential for recipients' to change their preferences over time (Supplementary Table S2). Our experiences with families who have

received iES/WGS suggest that persons may change their minds either for more or less results at different points in the process.[67] It is conceivable that an individual may wish to receive additional results if he or she has had a positive experience with receiving results. Conversely, an individual's initial enthusiasm for receiving results may be tempered after having a negative experience with receiving results. In our opinion, the time between expressing preferences and receiving results provides an important opportunity for recipients to seek expert guidance, obtain input from other family members (especially given that conflicts will arise more frequently in which knowledge of a genotype will mean by inference that other family members carry the same genotype), and ultimately to change their minds if they so desire. In contrast to the often time-sensitive context in which genetic testing and counseling occurs (e.g., reproductive decision-making, treatment decisions, etc.), iES/WGS results are less time sensitive and may benefit from a process that is recipient-driven, at his or her own pace. Individuals may also wish to have flexibility in the rate at which results are made available to them. In other words, some may wish to receive all results at once while others may rather receive results serially over time.

Second, a system must include information about the result that is "appropriate," that is information that is accurate, balanced, and easy to interpret—particularly any explanation of risk. This may be especially important because the meaning of results may differ depending on the recipient's personal and social context. Key considerations may include how results are described, the background information needed to interpret results, especially with regard to how a health condition is associated with a genetic result, and the steps an individual may wish to consider taking in response to a receiving a result. This results management framework is not meant to deliver health care treatment or specific recommendations, rather it is information that can be used and understood for its health implications much as other information can/should be used/interpreted. Most often it will require expert interpretation and contextualizing, but sometimes it won't.

Third, the scope and scale of iES/WGS results will require a system that enables more effective utilization of genetic counseling. There will still be a strong demand for genetic counseling that may outpace availability, but their efforts and work will be different in this new model. In the short term, health care providers (e.g., genetic counselors, clinical geneticists) will still deliver some information and provide decoding for people that need additional help understanding their results. To this end, in the context of a self-guided approach to managing iES/WGS results, genetic counselors may serve more as a interpretive safety net for recipients after their own initial review of results. For example, individuals may wish to check-in with their health care provider about a particular result to validate their own interpretations of the meaning of a result. Because management of iES/WGS results also requires a shift in approach from receiving results from a one-time exchange to an on-going process, genetic counseling will be likely needed by individuals at multiple times at a pace driven by recipients.

Fourth, a system should allow for the possibility of secondary audiences. Anyone with whom an individual might share their genetic results (family, physician, etc.) is a potential secondary audience for results return. Individuals may seek to share their results for a variety of purposes. Developing mechanisms to support recipients as they share results is a

high priority and will require the expertise of genetic counselors, health education and promotion specialists, clinicians including general practitioners, and family communication specialists. Given the diverse range of expertise necessary, a centrally coordinated system for returning results may be most efficient and effective for a recipient and their associated audiences.

Fifth, a system should increase opportunities for different racial and ethnic groups to receive iES/WGS results rather than exacerbate or create new health disparities. Many factors have been suggested to explain disparities in genetic test utilization and genetic research participation[68–72] including physician recommendations, mistrust of medicine and research, differences in genetic awareness and knowledge, and cultural differences about communalism, spirituality, and temporal orientation. We expect that many of these may be relevant and possibly heightened by return of iES/WGS results. Indeed, recent studies suggest that interest in receiving results may be substantial among minority communities participating in research.[73,74] Research involving diverse populations is clearly necessary to enable adequate interpretation of iES/WGS. Any approach to managing iES/WGS results will need to be tailored to maximize utility in different ethnic and racial communities.

Summary

There will be many important challenges to successful implementation of a system to facilitate self-guided management of iES/WGS results. First, it has been argued that the offering full iES/WGS results for return, particularly risk variants for complex diseases and/or results that are not clinically actionable, will be overwhelming and anxiety provoking for many individuals. We think that this argument is overly paternalistic, and that the question should not be how do we limit what ES/WGS results a person can receive, but how we can improve access and translation, through effective education, meaningful communication, and the preservation of individual preferences. Furthermore, a self-guided management system can allow participants to titrate results over time according to their preferences, and therefore may be an improvement over the presentation of all results en mass. However, we need empirical data about the barriers to and limitations of different people's capacities to understand genetic information in various contexts. Studying the use of such systems for results over time, and correlating usage with impacts and outcomes, will help us improve our approaches that maximize benefit and minimize harm, while preserving individual autonomy.

Second, a self-directed results management system has to be affordable, and strategies for payment and reimbursement of use of the system over time, perhaps most explicitly in the clinical setting, will need to be developed that allow for the broadest possible access. Another broad challenge that may be exacerbated by the widespread availability of iES/WGS is the high cost of healthcare and by extension to payers similar to the way that direct-to-consumer genetic testing has been described as "raiding the medical commons."[75] While this concern is by no means unique to genetic information, we expect that current standards for downstream evaluation of genetic findings will continue to guide medical management but that the possibility of increased health care utilization resulting from increased access to genetic disease risk information will need to be considered. However, we

think that self-guided management systems approach can be less expensive than traditional models of returning results, both for management of targeted genetic testing and iES/WGS results, and may indeed by the only way to effectively control costs.

We have focused on explaining the conceptual underpinnings of a self-guided iES/WGS results return model agnostic of the setting (e.g., clinical, research, etc.) in which it might be applied. We stress that the expectations of patients and research participants differ, as do the responsibilities and obligations of clinicians and investigators. These differences will undoubtedly influence the operationalization and impact of self-guided iES/WGS result return. A researcher has a limited obligation, if any, to care for or provide benefit to research participants and the offering of iES/WGS results is likely still optional in most research contexts. In contrast, a care provider is ethically bound to act in the best interests of a patient and to do so within a highly complex technical, regulatory, legal, and social framework. Accordingly, implementation of self-guided iES/WGS results management, even in part, raises many questions, the answers to which likely will require further innovation to interface with much less replace traditional models of results return in a clinical setting. For example, who should bear the responsibility of maintaining a person's sequence data (e.g., storage and security), updating derived genetic results, and managing related medical follow-up? Would these be the responsibility of the service lab that did the sequencing? A separate service that performed annotation and/or interpretation? Or rather of the ordering provider or the institution where the test was ordered? Or the responsibility of some combination thereof?

A self-guided model of results return might require a shared set of responsibilities for laboratories, providers and patients. For example, initiating care based on a result returned might be one shared responsibility. The laboratory and provider might be responsible for providing customary care codified initially through practice guidelines (e.g., ACMG Policy Statement Points to Consider in the Clinical Application of Genomic Sequencing) and results that providers will be strongly encouraged to return. Responsibilities for initiating care based on secondary results returned would be shared. A provider might initiate care because he or she recognizes that a result in the medical context of his or her patient, requires a decision about preventive care or medical management of an existing condition. Alternatively, a patient, having reviewed their results, might seek follow up medical care or advice from his or her care provider. While the details of this scenario may vary, most noteworthy is that responsibility for initiating care, medical decision-making, an individual's health, etc. are all shared and one in which patients under a self-guided management model have a much greater role and greater autonomy than in the past. In this sense, relationships between patients and providers will by necessity become more interactive and longstanding. Accordingly, a model of self-guided iES/WGS results management could be the engine that fundamentally alters the way health care providers and institutions utilize laboratory tests and interact with clinical service laboratories.

Finally, some may argue that such an approach to iES/WGS results management is an extension of a false promise of personalized genomics, and may contribute to genetic determinism and hype about the potential benefits of genomic information. Such hype, they would argue, impedes justice by inappropriately allocating health care resources to

genomics rather than other critical health care resources. We disagree strongly, and think that such an approach and system can in fact be an important deterrent to misunderstandings about the potential benefits of genomic information, and can provide important, accessible information to individuals that may decrease, rather than increase, potential unnecessary burdens on the health care system, including unnecessary testing, and diagnostic odysseys. Instead health care encounters will be focused on the translation of genomic information, along with environmental exposures and personal lifestyle choices, in the broader context of assisting individuals make informed decisions about reproductive planning, prevention, diagnosis and treatment—in other words decisions about how to best manage their health capitalizing on only the genomic information they choose to access.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank the families with whom we have worked and have thus contributed to our thinking about ES/WGS results management. Support for this study was provided by the National Institutes of Health (5R00HG004316-04 and 1UL1 RR025014) and the National Children's Study.

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