Group A: No specific medical management can be offered to change the most significant, serious, or debilitating aspect of the disease (scores 9–10). Genes in published Bin 2c scored a mean of 9.3, suggesting some agreement on lack of treatability. However, we have 1,445 OMIM entities that also have general lack of actionability. Not all are life threatening, but all are untreatable.

Group B: Limited medical management is available, but the most serious aspects of the disease are not improved or fully prevented (scores 6–8).

Group C: Medical interventions are recognized as helpful; however, medical interventions do not eliminate all the medical issues and risks associated with the disease (scores 3–5). Published Bin 1 had a mean score of 3.9, trending toward treatable but also indicating that the actions that can be taken incompletely address some disorders.

Group D: Medical treatments and management for the disease are available that essentially restore ideal health (scores 1–2). Thirty-two entries from Bin 1 were in this category.

Multiple other domains were scored in TRuST, including inheritance, childhood lethality, progressive nature, organ system/function affected (includes dementia), and severity (although it remains to be seen if it can be validated). One might want to know if an untreatable condition is very serious or rather minor, if opting in or opting out of knowing one's status. There are no data to support one classifying system over another, nor have real-world preferences and needs been distilled for clinical WES/WGS. We will share lessons learned as we refine and attempt to validate the TRuST domains to determine what is useful or useless to provide useful choices for our patients.

DISCLOSURE

The authors declare no conflict of interest.

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Response to Lindor *et al.*

To the Editor: We greatly appreciate the comments of Dr Lindor and colleagues in the letter titled "Preserving Personal Autonomy in a Genomic Testing Era"[1] regarding our approach to managing incidental findings from genome-scale sequencing.[2] We wholeheartedly agree that a consensus-based approach for determining how to handle the broad spectrum of incidental findings is unlikely to satisfy all constituents in the long term. Likewise, we are in complete agreement that patient preferences should play a central (although not exclusive) role in determining the return of results. Indeed, our "binning" approach attempts to balance the ethical responsibilities of the clinician (such as the duty to warn) with the autonomy of the patients to determine what information they want to know and what information they prefer not to know.

There are certainly many valid approaches to dividing the genome into categories that can be used to manage the return of incidental findings, but we strongly believe that some measure of clinical actionability will be a critical parameter in any successful strategy. In our approach, Bin 1 can be considered the category of incidental information in which the degree of clinical actionability invokes a duty to warn that supersedes patient preferences. Bin 2 contains the bulk of incidental information with limited clinical actionability that some patients may desire to know, whereas others may not, which is the very definition of individual informed decision making. Of course, there will be differing opinions about where to draw the line between Bin 1 and Bin 2, which is essentially the crux of the problem with consensus-based approaches to "binning" the genome. Instead, as pointed out by Lindor and colleagues,[1] there is a continuum of actionability.

We are therefore intrigued to hear about the efforts at the Mayo Center for Individualized Medicine to develop the Tailored Result Selection Tool with a scoring system for "actionability," and we were gratified to see that our provisional bin assignments correlated reasonably well with the Mayo group's actionability scores. Our group has come to the very same conclusion that a semiquantitative measure is required to score the clinical actionability of gene–phenotype pairs in order to categorize them in a transparent and evidence-based fashion. We have focused on four key components of clinical actionability: (i) the severity of the threat to health for an undiagnosed individual carrying an incidentally identified deleterious allele; (ii) the likelihood that a serious threat will materialize, akin to penetrance; (iii) the effectiveness of interventions at preventing harm from occurring; and (iv) the acceptability in terms of the burdens or risks placed on the individual. These components of actionability have also been adopted as part of an evidence-based framework being developed by the Evaluation of Genomic Applications in Practice and Prevention working group[3].

Our local "binning" committee is now systematically scoring gene–phenotype pairs much in the same way as described by Lindor and colleagues.[1] In the process, we have revised the

bin assignments of some genes. We ultimately plan to use the semiquantitative actionability scores to set a threshold for Bin 1, and we anticipate exploring different weighting systems for the key components of clinical actionability and/or thresholds to define Bin 1 in different clinical contexts. Thus, one could set a very high threshold such that Bin 1 contains very few genes, leaving more genes in Bin 2 for individualized decision making. One could also imagine using the continuum of actionability scores to facilitate individual decision making regarding return of results. It will be fascinating to hear more about the Tailored Result Selection Tool system, and we very much look forward to the results and lessons learned.

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Avicenna's view on medical genetics

The chief landmark in the history of genetics is most likely the work of Gregor Mendel on pea plants in the 19th century, which later was translated to the concept of Mendelian inheritance in medical genetics.[1] However, early theories of inheritance were described by Hippocrates (460–377 BC) and Aristotle (384–322 BC), and their observations formed the basis of the study of inheritance by the principles of science.[2]

Islamic medieval physicians also pointed out the hereditary nature of some disorders such as hemophilia, noted by Albucasis (936–1013 AD).[3]

We studied Avicenna's (Persian physician, 980–1037 AD) views on different aspects of medical genetics by reviewing his *Canon of Medicine*[4] and searched MEDLINE for relevant hereditary and congenital concepts and descriptions of temperament. We also investigated *Zakhireh-kharazmshahi* by Gorgani (a Persian physician inspired by Avicenna, 1041–1136 AD),[5] which is a comprehensive source in traditional medicine.

Three main topics in the *Canon*, including temperament (*Mizaj*) and its uniqueness in each individual, hereditary and congenital disorders and their classification, and the rationalization for inborn malformations, foreshadow the development of the field of medical genetics. Considering the significance of temperament in traditional medicine, Avicenna emphasized the individuality of people based on their unique temperament, which would later correspond to the unique genetic makeup of each person and presage the central notion of interindividual variation so critical to the work of Darwin.[2] In addition, Avicenna discussed the congenital versus acquired nature of some disorders such as hearing loss and muscle problems in his book and, in some instances, described their severity and differences in more detail.[4] In discussing the transmission of diseases from person to person, he named six conditions, including premature baldness, under the category of hereditary transmissions.[6]

Avicenna also classified congenital malformations into four categories: errors in form (such as broad head), errors in passages (such as stricture of the trachea), errors in cavities (cavities of the heart, for instance), and errors of surfaces (roughness and smoothness) (**Table 1**).[4]

On the cause of deformities, he explained that some come into play from the beginning because of a defect in the formative

Table 1 Avicenna's classification of congenital malformations into four categories: errors in form, errors in passages, errors in cavities, and errors of surfaces

Group	Subvarieties	Examples
Errors in form: here the form is changed from its natural grace to an extent that impairs its utility	Deviation from a natural straightness, straightness of a naturally curved line, squareness where there should be roundness, rotundity where there should be squareness	Head broad and round, with ossified sutures to an extent hindering mental power, curved shinbones, genu valgum, clubfoot, pupils congenitally elongated or slit-like or small, great rotundity of abdomen
Errors in passages	Too wide, too narrow, occlusion	Wide pupils, varices, aneurysms, the dilated blood vessels in pannus, small pupils, narrowed eyes, stricture of trachea or bronchi, stricture of esophagus, occlusion of venous orifices
Errors in cavities	Too large (distended), too small (contracted), obstructed and overfull, emptied	Distended scrotum, contracted stomach, contracted cerebral ventricles in epilepsy, obstruction in cerebral ventricles in apoplexy, cardiac cavities emptied of blood by reason of excessive joy or extreme pain
Errors of surfaces	The normal roughness replaced by smoothness, the normal smoothness becomes rough	At the orifice of the stomach, trachea, fauces