

Future on a Flashdrive: Timely Considerations for the Imminent Adoption of Whole Genome Sequencing in Pediatric Healthcare

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Executive Summary: In just twenty years, humanity has progressed from the first sequenced human genome to the ability to sequence one in a matter of hours and for only hundreds of dollars. This rise in affordability and speed has enabled physicians to use whole genome sequencing (WGS) as a diagnostic tool, particularly in cases of rare disease in pediatric patients where it has already demonstrated immense potential. However, such a rapid development in technology powerful enough to unlock a person's genetic information has also led to necessary questions regarding when and how it is applied. In this assessment, we discuss the implications of WGS adoption in pediatric healthcare, focusing specifically on ensuring ethical and equitable collection and communication of genomic data as well as the need for secure and accessible data storage methods. We identify several key areas where further policy is most pressing and provide value-driven recommendations centered on guaranteeing pediatric patient safety, equity, and empowerment during the broader introduction of WGS tools. In particular, we advocate for legal frameworks that limit present usage of WGS to only those patients with a clear and present need, guidelines that expand the labor force that can conduct WGS, increasing access and equity, improved standards for storage, access, and sharing of WGS data, and finally expanding Medicaid coverage to include WGS use in critical care settings.

I. Background

A patient's genome represents about 700 megabytes (Kasilov, Drobintsev, and Voinov 2021) of personal health data that can indicate anything from that person's susceptibility to a particular disease (Cho and Gregersen 2011; O'Donnell 2011; Geschwind and Flint 2015) to how responsive they would be to specific treatments (Rosenquist et al. 2022). This wealth of genetic information holds immense promise in the evolution of personalized medicine and has driven innovation in genome sequencing technology. Sequencing an entire human genome, which once cost The Human Genome Project (HGP)

nearly \$3 billion and took thirteen years, can now be done for \$1,000 per patient in a matter of days, and could soon be done for closer to \$100 (Pennisi 2022). This rapid improvement in affordability and rate of sequencing signals the impending reality of utilizing Whole Genome Sequencing (WGS) as a routine medical tool to aid diagnosis and inform treatment design.

DNA sequencing as a technology was first developed in the early 1970s (Heather and Chain 2016) and its use in medical practice over the following decades was primarily limited to targeting specific genes of

interest (Lorentz et al. 2002; Wright, FitzPatrick, and Firth 2018). In particular, monogenic diseases, which are diseases attributable to a single gene mutation, saw significant increases in early detection and diagnosis. Such monogenic diseases include cystic fibrosis (linked to the CFTR gene), sickle cell anemia (HBB), and certain forms of breast and ovarian cancers (BRCA1 and BRCA2) (Prakash, Moore, and Yáñez-Muñoz 2016; Narod and Foulkes 2004). Unfortunately, the targeted screening of specific genes can often fall short of providing a diagnosis, as many diseases are not monogenic and have much more complicated genetic relationships. It is in these instances that the demand for WGS lies. For example, many forms of cancer are the result of mutations in any number of genes related to the regulation of cell division and have no singular diagnostic gene. However, the analysis of the overall instability of a patient's entire genome (how many mutations and genomic defects are present on average) can be indicative of how that patient will respond to certain treatments (Rosenquist et al. 2022). In addition, targeted sequencing of a select few genes is limited to circumstances in which the physician has a probable set of diseases to assess. In the case of more rare genetic diseases, it is much more efficient to sequence the entire genome and compare the results against a larger database of genetic disease profiles (Wright, FitzPatrick, and Firth 2018; Lionel et al. 2018). Both of these applications, assessment of whole genome characteristics and broad screening for rare disease diagnosis, represent the unique potential that WGS possesses for revolutionizing healthcare.

i. Clinical genomics and pediatric medicine

The application of WGS in pediatric medicine is particularly necessary. The majority of rare genetic disease burden rests on pediatric cases, with nearly 1 in 3 child fatalities attributable to a rare genetic disease (Eurordis 2005; Ferreira 2019; Stevenson and Carey 2004). Additionally, since children have a much longer length of life after diagnosis than adult patients, identifying and treating these diseases early in the pediatric stage presents greater long-term benefit both in improved quality of life and in cost effectiveness, an important part of working WGS into current healthcare payment infrastructures (Dimmock et al. 2021; Seydel 2022). Such extensive promise of positive health and financial returns have led to discussions surrounding

the potential use of WGS as a standard clinical screening test in all newborns (Goldenberg and Sharp 2012; Remec et al. 2021), but for the moment, the pilot studies incorporating WGS into pediatric care have primarily focused on patients already presenting significant disease symptoms (Malinowski et al. 2020). These pilot studies have had considerable success in diagnosing patients, improving health outcomes, and bringing down the overall cost of care (Dimmock et al. 2021; Sanford et al. 2019; Halabi et al. 2022). One such program deployed at the Pediatric Intensive Care Unit (PICU) at Rady's Children Hospital in San Diego found that 45% of their 38 patient study group were able to be diagnosed following WGS (Sanford et al. 2019). 82% of the diagnoses led to changes in treatment and disease management following discharge, while 24% of the diagnoses led to a change in disease management while still in the PICU (Sanford et al. 2019). The positive results of this study led directly to a wider scale study within the California Medicaid program. This study found that 40% of the 184 members of their patient population received a diagnosis for their symptoms, with 32% receiving a change in treatment plan (Dimmock et al. 2021). These studies targeted exclusively acutely ill populations, but some preliminary studies exploring the use of WGS as a test included in standard newborn screening (NBS) have been conducted (Bodian et al. 2016; Ceyhan-Birsoy et al. 2019). Such studies have found that WGS can be integrated into already existing NBS procedures and can serve to identify diseases that may not be detected by current NBS tests. However, the financial benefit and ethics of introducing WGS into healthy pediatric populations are topics of ongoing debate (Remec et al. 2021; Woerner et al. 2021).

ii. Appropriate use of WGS in newborn screening

The decreasing cost and increasing technical capacity of WGS technology enables a future where WGS is no longer a last-ditch option after standard diagnostic methods have failed, but a frontline diagnostic, and eventually a universal newborn screening tool. This transition would represent a fundamental shift in the nature of newborn screening programs relative to current standards. Current newborn screening programs are generally confined to conditions with a pediatric onset, for which demonstrated effective treatments are available, and for which genotype is strongly

predictive of disease phenotype (Howard et al. 2015). Further, screening tests are designed to establish risk, and are followed by confirmatory diagnostic testing (Howard et al. 2015; Kingsmore and Saunders 2011). Because of the low risk of screening, and the clear benefit to the newborn, many screening programs operate under an opt-out consent paradigm in which parents are not asked to consent to newborn screening but rather given the right to object (Howard et al. 2015). In contrast, WGS identifies a much broader range of conditions, with greater variability in the genotype-phenotype relationship (Kingsmore and Saunders 2011). There are also significant privacy risks and risks associated with misdiagnosis from WGS—making WGS an inappropriate candidate for an opt-out consent process. Further, WGS can identify conditions for which confirmatory diagnostic testing is not available (Kingsmore and Saunders 2011). Additionally, WGS is likely to have a lower positive predictive value as a screening tool for all patients than as a diagnostic tool for patients referred based on symptoms (Johansen Taber, Dickinson, and Wilson 2014). As most WGS studies have not been performed in a general population, the full risks of this have yet to be elucidated (Johansen Taber, Dickinson, and Wilson 2014). Were WGS for newborn screening to be implemented in general populations, the consequences of this paradigm shift would need to be examined and safeguards implemented.

iii. Outstanding scientific and ethical concerns of clinical WGS use

When considering the application of WGS in clinical settings, one major concern is that disease-linked variants may be identified in a patient's genome that are not currently presenting symptomatically. Even if a disease-linked variant is present in a person's genome, a number of regulatory systems, called the epigenome and transcriptome, affect whether this gene is expressed (Martinez-Delgado and Barrero 2022). The result of this is that a genetic professional needs to first, correctly identify a disease present that the patient is presenting symptoms for and, second, determine whether additional disease-linked genes present a probable and treatable threat to the patient's health. On the one hand, reporting information—even that unrelated to the initial presentation—may be of great benefit to the patient or family. For example, if a pediatric

patient is observed to have an oncogenic BRCA1 or BRCA2 mutation, the practitioner may have an ethical obligation to ensure the child's parents are receiving regular cancer screenings. In contrast, reporting information the family did not anticipate—and would not have chosen to receive—that also does not necessarily present immediate or actionable danger could ultimately be considered a violation of the patient's autonomy and a failure in the informed consent process. Further, the need to search for and report secondary findings increases the cost of the testing process. Reporting health information to patients without the infrastructure for genetic counseling, relevant treatments, and appropriate long-term monitoring risks psychological harm. This harm is a form of malfeasance and should be avoided. In the weighing of these concerns, it is commonly accepted that conditions with a childhood onset and clear treatment options should be reported (Dimmock 2012). The greater challenge is determining what to do with adult-onset conditions.

For some, the possibility that adult onset conditions could impact health decisions of other family members, like the discovery of BRCA carrier status, is sufficient to necessitate reporting (Dimmock 2012). This policy is not without downsides. For BRCA, increasingly, testing is not recommended in a patient's early 20's or before because of the harms associated with the "previvor" experience (Dean 2016). Thus, the child's right to an open adult future, free of carrier information they may not want, is at odds with the benefit to family members who could benefit from knowing their status. Further, family members seeking treatment for a child are not anticipating information about themselves and have not received the counseling or support that would typically precede BRCA testing (Schneider 1997). Thus, the reporting of secondary findings is not an absolute good and the benefits associated with knowing any particular secondary finding must be weighed against the risks.

Even more ambiguous than what to do with secondary findings is how to treat findings of unknown significance. On the one hand, reporting these findings to patients risks inappropriate treatment or overtreatment, in the cases where a genotype finding is not accompanied by a medical indication. In favor of not reporting these findings, as

much as 27% of the interpretations in literature do not stand up clinically (Kingsmore and Saunders 2011). Further, genetic findings often come with stigma, particularly for pediatric patients who then live their formative years in the shadow of an anticipated medical condition. This phenomenon, termed genetic determinism, should be given particular weight when the likelihood of disease is unclear, and the significance of the finding is incompletely understood. Because there is significant inequity in ethnic representation in reference genomes (Halabi et al. 2022), reporting genetic information for which the genotypic-phenotypic relationship is not fully elucidated risks giving results to some patients that are less accurate than those for other patients. Alternatively, WGS is especially useful in situations where the presentation is inconclusive and/or other diagnostic tests are not available (Kingsmore and Saunders 2011; Biesecker 2012)—the exact kinds of situations where it is likely there isn't a clear genotype-phenotype connection—and failure to report ambiguous results could decrease the clinical value of WGS. In addition, reporting results of unknown significance allows for monitoring of the patient, research which can establish the significance of the finding. There is a lack of consensus regarding how to report findings of unknown significance (Dimmock et al. 2021; Evans and Rothschild 2012), but it is essential that these standards be established.

iv. Cost-benefit analysis of WGS in pediatric medicine

One of the major benefits for using WGS technology in acutely ill pediatric populations is that it lowers healthcare costs substantially, both during the initial hospital stay as well as over the course of the patient's life. Pediatric patients with genetic disease are often extremely costly to hospital systems due to their extended stays in neonatal or pediatric intensive care units (Farnaes et al. 2018). The study mentioned above in the California Medicaid system, for instance, led to cost savings between \$2.2-2.9 million, primarily due to reduced hospital stays attributed to expedited diagnoses and treatments, although minimizing tests and procedures that would have been ineffective also contributed to lowering costs (Dimmock et al. 2021). Another 2018 study found that in 42 infants who underwent WGS, 31% experienced a positive change in medical/surgical management and 26% avoided

morbidity. This reduction in morbidity not only saved lives, but was also accompanied by a reduced cost of up to \$2 million (Farnaes et al. 2018). A study from 2020 presented similarly convincing findings as they showed that in only a single patient's case, WGS saved the hospital approximately \$181,141 in medical costs when accounting for the cost of WGS (Grosse and Farnaes 2019). They also found that WGS avoided an average of 38 days in the hospital which also has an economic impact on the work output of the parent (Precision Medicine at UCSF 2020). Beyond economic benefits following WGS, infants and parents are also often spared painful and risky procedures, time in the hospital, and significant emotional turmoil.

The cost-benefit savings of this is not as clear when looking at the use of WGS as part of a regular screening routine in pediatric patients that are not acutely ill. The costs of genome sequencing for healthy children (\$7284) were approximately the same as that of the standard of care (\$7355; Incerti et al. 2022). Therefore, this study suggests that the use of WGS in healthy pediatric populations is cost neutral. However, as the diagnosis also has the potential to catch severe genetic abnormalities before the symptoms arise, it may be a cost-saving procedure in the long term.

v. Equity of WGS access

It is important to note that the large majority of studies and data presented in the previous section were conducted in the United States and other western nations and therefore are not a wholly accurate representation of the costs and procedures that need to be considered in other regions of the world. This geographic restriction is largely due to the upfront costs of acquiring WGS technologies. Despite the decline in the cost per sequence, the initial investment in technology and infrastructure remains high. This often presents an insurmountable barrier to access in lower resource settings. Therefore, despite potential cost savings, significant investments in infrastructure, trained staff, and other technological equipment are needed to make WGS a reality in low-resource settings (Halabi et al. 2022).

Global distribution of WGS is heavily skewed towards the global west with many centers offering WGS in Europe, North America, and Australia (Halabi

et al. 2022). This leaves many populations that are heavily impacted by genetic disease burden, such as Middle Eastern populations, woefully underrepresented. More than 80% of genomics studies have been conducted in populations of European descent (Fatumo et al. 2022). Individuals of Middle Eastern descent, on the other hand, represent just 0.01% of genome-wide association studies' data and less than 1% of all publicly accessible sequencing datasets (Halabi et al. 2022). This skewed representation and lack of diversity in genetic databases decreases the accuracy of WGS for underrepresented individuals: researchers are using a reference genome that is inaccurate for their genetic nuances. This imbalance needs to be addressed to improve equity and access (Fatumo et al. 2022).

Achieving more equitable access to WGS is of two-fold importance. First, it can help bring the potentially lifesaving benefits of WGS to pediatric populations on a global scale (Jooma et al. 2019). This then has the potential downstream benefits of reducing costs and infant mortality and morbidity, as has been shown is possible in many US-based studies (Farnaes et al. 2018; Grosse and Farnaes 2019; Seydel 2022). Second, it is also beneficial to the scientific community to understand human disease through the lens of diversity as genetic background impacts how different people respond to disease (Fatumo et al. 2022). The potential scientific insights gained by diversifying sampled populations may therefore provide essential data to help make future drug and therapy discovery and development applicable to the broadest range of patients (Fatumo et al. 2022). This diversification hinges on ensuring access to WGS infrastructure in as many countries as possible.

Individuals in low resource settings that are able to access WGS technology are often subject to much longer turnaround times of up to four weeks as samples are shipped internationally (Halabi et al. 2022). In comparison, if the technology were located in the same country, testing and diagnosis can occur within a matter of one to four days, a difference that is life-saving to many children who have a severe genetic disease. This lack of access leads not only to delayed diagnosis and treatments, but also difficulties in communicating the results of the sequencing to the affected individuals (Halabi et al.

2022). A 2022 study in the United Arab Emirates highlights the potential of having co-located sequencing technology as they were able to sequence and diagnose five pediatric patients within 37.4 hours as opposed to having weeks of delay. As such, significant investments in genomic infrastructure and expertise would be needed within local healthcare institutions which may not be feasible for less economically advanced settings as costs of setting up genomic facilities can exceed \$3 million (Halabi et al. 2022). Additionally, recruiting, training, and retaining such skill sets is a major challenge in underrepresented, low resource regions such as the Middle East. Halabi et al., suggest in their 2022 study that WGS will be limited to highly specialized tertiary centers but that these should be located within each country. While this does not yet promise access to all, it may help to improve access within less economically developed countries, decrease turnaround time, improve communication, and improve the ability to recruit and retain multidisciplinary skill sets (Halabi et al. 2022).

Another obstacle towards WGS equity is the availability of trained physicians. Due to their extensive training and expertise, a medical geneticist (a medical doctor specializing in genomic medicine) would ideally facilitate care. However, the current size of the medical geneticist labor force is not large enough to meet the increasing demand for genomic medicine, even in high-resource countries (Jenkins et al. 2021; Maiese et al. 2019). One proposed solution to this labor shortage is to make use of genetic counselors and specialized nurse practitioners to satisfy some demand, such as in cases where the genetic conditions are identifiable and easily treated (Stewart and Svihovec 2022). More complicated cases with unclear diagnoses or complicated management could then be prioritized for referral to a medical geneticist. Additionally, the use of telehealth is an important tool to meet demand, particularly in rural settings, as most medical geneticists tend to be concentrated in large urban centers (Jenkins et al. 2021; Penon-Portmann et al. 2020; Maiese et al. 2019). Some surveys have found that genetic counselors are much more likely to use telemedicine than medical geneticists (Maiese et al. 2019), but the overall use of telemedicine was low among all genetic health specialists, and increased use should be encouraged to meet

encroaching demand and ensure access to care regardless of geographic location.

vi. Data considerations

Despite the increases in speed and scope of testing, as well as driven-down costs of sequencing, the size and sensitivity of genomic data makes designing scalable and secure methods for data analysis, storage, and sharing no easy task. Although the genome alone consists of 700 megabytes of information, the raw sequencing files created from a single person can range from tens to hundreds of gigabytes depending on the sequencing technology used and file type (Kasilov, Drobintsev, and Voinov 2021). This is largely due to storing multiple overlapped reads to ensure accuracy. Furthermore, a sequencing workflow will often result in a variety of different files, such as the aligned sequence (e.g., SAM) and the variant information (VCF). It is clear that WGS at scale results in massive datasets, which necessitates creative solutions for storage and analysis workflows, often using cloud architectures (Tanjo et al. 2021).

In addition to being big data, clinical genetic data is also identifiable and personal, which means it is subject to a complex and often vague network of laws and policies (Mitchell et al. 2020). The situation only gets more complicated when you consider the unique challenges of pediatric data, where there is an increased imperative for regulation and a need for transitioning consent and data ownership.

Despite these challenges, some progress is being made. In the research setting, general frameworks for data handling are starting to coalesce, led by organizations like the Genomic Alliance for Global Health (GA4GH; Rehm et al. 2021). However, in clinical settings, healthcare practices surrounding genomic data are still quite scattered and heterogeneous. There is also a lack of data sharing between the clinical and research environments, particularly in the pediatric setting, which may impede progress in discovering new gene associations.

The use of a patient's genome in wider research studies should be carefully considered as a possibility. New understandings of disease and human health can be gleaned from the analysis of large pools of population genetic data. Already, there

are ongoing efforts to collect whole genomes from both healthy and ill individuals at large, population-sized scales. A few such initiatives have been completed, such as the 1000 Genomes Project (Auton et al. 2015), but many more are underway, including the GenomeAsia 100K Project (Wall et al. 2019), the U.K. 100,000 Genomes Project (Turnbull et al. 2018; Smedley et al. 2021), and the EU 1+ Million Genomes (1+MG) Initiative (Saunders et al. 2019). Sharing data as personal as a genome can be an intimidating prospect for many patients, but the pooling of this data into such "biobanks" can be the difference in how quickly new breakthroughs in diagnoses, treatments, and cures are discovered.

Currently, these biobanks are spread across the world, and are thus covered under various legal frameworks and operating under different institutional policies. Such a situation is not amenable to collaborative genomic research. To address this, consortiums like the GA4GH have been working to create standards for working with genomic data that ease data sharing and access. In part, these standards aim to promote FAIR data sharing: Findability, Accessibility, Interoperability, and Reusability (Wilkinson et al. 2016). For example, GA4GH aims to address interoperability by maintaining and promoting file storage specifications, like BAM/CRAM. Their guidelines and standards go far beyond just file storage, spanning the whole data life cycle from data collection to storage to analysis. Their policies give guidance to data custodians wishing to build secure infrastructures and define structures for access requests and approvals, facilitating researchers who wish to access such sensitive information (Rehm et al. 2021). Importantly, GA4GH standards are being taken up by major international genome projects, notably the Beyond 1 Million Genomes Project, which is the first phase in implementing the European 1+ Million Genomes Initiative (Spalding et al. 2021).

II. Policy recommendations

As WGS becomes more common in clinical settings, it is critical that sound policy is enacted to ensure accurate and ethical collection, storage, assessment, and reporting of genomic data. Recent research has supported the need for a paradigm shift in WGS result reporting from a single time-point to considering WGS data as a lifelong and dynamic

resource for patients to reference (Yu et al. 2013). While this would necessitate a considerable increase in infrastructure across every level of WGS data collection, storage, assessment, and return, including the resources to obtain consent and ensure patient control at each of these steps, this new system has great potential to increase patients' ability to benefit from their genomic data.

The following recommendations highlight the policy goals that would be important to consider during a transition to broad scale WGS in children and newborns and examine the implications of using WGS data as a patient-controlled lifelong resource in this context.

i. Establish legal frameworks to ensure whole genome sequencing is presently only used in patients presenting clear and severe clinical symptoms

To avoid disclosing non-emergent information about a patient's future that may have a detrimental effect on their well-being, legal safeguards should be put in place to prevent WGS results being used outside of diagnosing symptomatic illness. In the United States, this would be most readily done via action taken by the state medical boards. Many state medical boards are empowered to dictate medical practice regulation within the state, and could mandate that WGS technology only be applied for symptomatic diagnosis. Possible resistance to this action may come from several groups. First, physicians who are concerned that over-regulation inhibits their ability to provide optimal care to patients and their families. While this is a laudable concern, it is unlikely that instances in which pediatric patients face a present danger would not already qualify for symptom-driven WGS, and therefore face no such restriction. Another group opposed to such regulation may come in the form of those who argue that individuals have a right to access their medical information, including their genome, and any possible predictive insight. This argument has merit, but in the case of pediatric healthcare, whose patients cannot properly consent to the practice, it loses weight. One possible solution is to limit the restrictions only to pediatric cases, and have a less regulated practice for informed adults. Finally, there may be some who find an executive agency limiting a practice via executive fiat to be too "undemocratic." State legislatures, however, are empowered to pass laws regarding the use of specific medical

procedures and can do so if the state medical board is unwilling or unable.

An additional compromise if a ban is deemed too restrictive could be to ensure a comprehensive informed consent process takes place before completing WGS. Such a process could require patients or guardians consent to each type of information that they may receive: that which presents an immediate medical danger, that which presents an uncertain danger, that which presents a probable danger much further in the future, and that which may affect loved ones, possibly sooner than the patient. For each of these, the potential benefits and risks can be provided to the patient, along with possible alternatives (such as having the parents receive separate genetic screening rather than using the child's information). Such a requirement, while still permissible enough to facilitate patient regret or anxiety, would add considerable patient protections and empowerment compared to the current policy landscape.

ii. Establish guidelines for how Nurse Practitioners and Genetic Counselors can serve routine cases and promote training of genetic specialists to prepare for increased demand of genomic medicine and counseling

To address issues surrounding the shortage of medical geneticists, state medical boards and state legislatures should make efforts to remove any existing red tape that may inhibit genetic assessments from nurse practitioner- or genetic counselor-led clinics. This may come in the form of the state medical board specifying and expanding licensing standards related to the practice of genetic medicine or the state legislature modifying the state medical act, the laws which typically regulate medical practice within a given state. However, since the use of WGS as a diagnostic tool is largely still developing, this should be preceded by a more specific analysis of best practices conducted by a professional society such as the American College of Medical Genetics and Genomics (ACMG), or by the National Academy of Medicine (NAM). Both the ACMG and NAM have published perspectives and recommendations on the clinical applications of WGS before (Miller et al. 2021; Manickam et al. 2021; Murray et al. 2018) but could contribute substantially to the development of clinical accessibility of the technology by outlining best

practices for incorporating a broader labor force that would include nurse practitioners and genetic counselors. Once such recommendations are more explicitly made, state medical boards and legislatures could then act on the appropriate policy changes. This avenue could ultimately increase accessibility of WG, which is critical not only to the broad adoption of the technology, but also to the equitable distribution of its benefits.

iii. Develop robust systems for de-identification and sharing of clinical data with biobanks/research

As previously discussed, there is a path forward on growing genome biobanks and building better architectures for data handling and access, clearing some of the bottlenecks which exist for gene discovery. However, much of this progress is in the research setting, and ignores what is being done on the clinical side; data sharing between the two groups is still minimal (Boycott et al. 2017). As a result, there is a wealth of data (genomic and clinical) being collected in healthcare or clinical research settings which could help better understand gene associations, but is not pooled with larger genome biobanks and not shared broadly with genetic researchers. This is especially true in the pediatric healthcare setting, where a significant quantity of information on children is collected but data sharing is rarely addressed (Rahimzadeh et al. 2018a). Naturally, this is largely because the privacy and consent considerations are complex, but that does not mean there is no way such collaboration could occur. To address this topic, a GA4GH working group created the Key Implications for Data Sharing (KIDS) framework for pediatric genomics, which details guidelines to facilitate a culture of data sharing that centers the needs of the children and ensures informed consent for all parties (Rahimzadeh et al. 2018b). However, such frameworks are only beginning to be discussed by institutional stakeholders and how responsible data sharing can be implemented is still a subject of much debate (Rahimzadeh, Bartlett, and Knoppers 2021).

As data sharing standards and technical infrastructure surrounding WGS become more robust, it is imperative that regulators in healthcare and clinical trial settings (the Office of Human Research Protections (OHRP), for example) encourage adoption of these tools. Naturally, the privacy and consent of patients always comes first,

but this does not preclude information exchange with larger scale research projects or biobanks. Consequently, anyone collecting new WGS data should address if and how their information collected can be shared with a broader community.

iv. Improve integration of WGS into electronic health records

In order to make genomic information exchange more straightforward, a first step is to ensure that results are processed and stored in a uniform way. To accomplish this, healthcare practitioners must be better enabled to implement WGS technologies in their everyday operation. This is no easy task: there are a large number of legal, ethical, and logistical complications brought about by the broad introduction of WGS into the clinic. One such complication involves the ability to access one's own genomic data. Some experts believe that patients having access to raw genome files can lead to misinterpretations given the complexity of such data, whereas others argue it is a fundamental right to have access to your own health data, which includes your sequenced genome (Schickhardt, Fleischer, and Winkler 2020). Looking at current practice, most institutions performing genomic sequencing do provide patients access to their raw data, although the timelines and formats vary widely (Narayanasamy et al. 2020).

A related question is how best to link patients' electronic health records (EHRs) and their genomic sequencing information. This is closely tied to the ethical questions of when to report results, which we have previously addressed. There are also technical hurdles in such linkages, given that electronic health records have no single standardized format and may not be readily adaptable to incorporating the complexities of genomic data (Kho et al. 2013). Nevertheless, work is being done on finding ways to combine these sources of information, for example by the eMERGE Network (McCarty et al. 2011). Some standards for structuring genomic results in the context of EHRs have been introduced (e.g., ISO/TS 20428), and initial studies have shown that these standards can indeed be adopted by modern hospitals, but the practice is not yet widespread (Ryu et al. 2020). Work must continue to both create more robust genomic standards as well as introduce policies and incentives that encourage hospitals to implement such systems. In the US, this effort would

likely be led by the Office of the National Coordinator for Health Information Technology (ONC), which has already begun work in this area through the Sync for Genes program (Garcia, Zayas-Cabán, and Freimuth 2020).

v. Introduce guidelines for ongoing stewardship of genomic data and appropriate recontact of patients

Another complication involves the use of previously collected pediatric WGS data over time. The storage of WGS can be beneficial to patients, as it allows their data to be re-analyzed in light of newer findings, leading to improvements in disease care and management (Aronson et al. 2012; James et al. 2020). On the other hand, there are particular privacy risks to the storage of identified genetic information that patients must be counseled on prior to consenting to WGS (Raffan and Semple 2011). Most pediatric patients are not old enough to consent to this risk at the time of data collection, but will later reach the age of consent while the data is still being stored. Thus, ongoing consent frameworks are important in pediatric genomics.

The process of storage, repeat analysis, and re-contacting of patients is resource-intensive, which increases the cost and decreases the accessibility of WGS (Aronson et al. 2012; Howard et al. 2015; Dimmock 2012). Further, there is a lack of consensus regarding which stakeholder has the responsibility to initiate the process of repeat analysis and reporting new findings to patients (Dimmock 2012; Johansen Taber, Dickinson, and Wilson 2014; Aronson et al. 2012). Some authors ascribe this duty to the patient's general practitioner (Richards et al. 2008). For others, this responsibility lies with the specialists who prescribed the WGS initially (Dimmock 2012). Alternatively, patients and their caregivers can be deemed responsible for periodically soliciting additional analysis of the data (Hirschhorn et al. 1999). Setting requirements for privacy precautions, and distributing responsibilities for re-contacting patients over time is essential as WGS becomes more ubiquitous. Once again, professional societies such as the ACMG should lead the way in developing guidelines for recontact of patients. Some recommendations have already been developed, for example by the European Society of Human Genetics (Carrieri et al. 2019), but much more discussion and research into best practices is needed.

vi. Expand Medicaid coverage to include WGS for critically ill pediatric care

Only recently in the United States, a number of state Medicaid programs, and for the first time a private insurer, have supported WGS use in critically ill neonatal and pediatric populations (Seydel 2022). Medicaid coverage is a valuable step towards ensuring access of WGS to any neonatal or pediatric patient in need. States that do not currently incorporate WGS into Medicaid coverage can do so either by decision from the state agency that administers Medicaid or via legislation from the state legislature. The federal government can also intervene and alter Medicaid federal funding to either incentivize or mandate that states incorporate WGS into Medicaid coverage. One such bill, the Ending the Diagnostic Odyssey Act of 2019 sponsored by Sen. Susan Collins, aimed to provide grants via The Centers for Medicare & Medicaid Services to encourage states to adopt WGS in Medicaid coverage, but was never voted out of committee. While federal grants could certainly contribute to the rate of Medicaid expansion, fiscally conservative policymakers have often been opposed to increased Medicaid coverage, even if federal funding is incorporated. However, prior studies have already demonstrated that incorporating WGS into Medicaid coverage ultimately saves the program money (Dimmock et al. 2021). It is not only moral but fiscally responsible for states to incorporate WGS into Medicaid coverage as soon as possible.

III. Conclusion

Innovation has drastically accelerated the timeline to implementing WGS as a regular diagnostic and screening tool in pediatric populations, but regulatory policy and infrastructure has not necessarily matched pace. Regulatory bodies, including state legislatures, medical boards, and health departments and the federal OHRP should establish boundaries limiting the application of WGS as a tool and the sharing of findings until further understanding of how best to apply this technology is established. This understanding can be elucidated through advisory committees established by the ACMG and NAM to more specifically advise on best practices when handling secondary findings, sensitive patient information, or how to expand and train a diverse labor force to handle rapidly growing demand. These bodies should advocate for the following policies:

- Legal frameworks should be developed ensuring WGS is currently performed only for patients with a clear and present need that cannot be achieved through other means.
- Guidelines should be developed for improving the capacity of practitioners, particularly utilizing the expertise of nurse practitioners and genetic counselors.
- Viable systems for secure data sharing between clinical and research settings should be invested in and subsequently deployed.
- Long-term integration of WGS data with current methods of storing and accessing medical information should be instituted
- Standards for reanalysis of WGS data and recontact of patients should be devised.
- Medicaid coverage should be expanded to include WGS for critically ill pediatric care.

The promise of WGS is enormous, and its adoption as a medical tool is a question of “how” rather than “if.” But that “how” has yet to be fully established, and stronger guidelines and regulations must be swiftly put in place to ensure that patient safety and comfort are prioritized, and that WGS will ultimately leave a positive impression on patients, their families, and society as a whole.

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