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Brief Report

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Addressing ethical and laboratory challenges for initiation of a rapid whole genome sequencing program

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Abstract

Rapid whole genome sequencing (rapid WGS) is a powerful diagnostic tool that is becoming increasingly practical for widespread clinical use. However, protocols for its use are challenging to implement. A significant obstacle to clinical adoption is that laboratory certification requires an initial research development phase, which is constrained by regulations from returning results. Regulations preventing return of results have ethical implications in cases which might impact patient outcomes. Here, we describe our experience with the development of a rapid WGS research protocol, that balanced the requirements for laboratory-validated test development with the ethical needs of clinically relevant return of results.

Introduction

Next-generation sequencing (NGS) technologies offer the potential to dramatically shorten diagnostic processes and improve clinical care [1]. Rapid whole genome sequencing (rapid WGS) is a recent NGS advancement, providing results in a week or less. Advantages of rapid WGS include rapid turnaround and the ability to identify many different genetic variant types. Clinical use of rapid WGS has been of particular interest for infants in neonatal intensive care units (NICUs) where mortality rates can exceed 10% [2], and the median daily cost of patients can exceed \$3,000 [3]. Rapid WGS in the NICU has shown immediate as well as long-term benefits on infant health, outcomes, and costs [4–8].

Currently, rapid WGS is available as a clinical test from only a few commercial laboratories in the USA. Recognizing this limitation, and the need for rapid WGS at our high acuity NICU, our goal was to develop and implement a rapid WGS test. However, our research development phase of rapid WGS required assessment of competing ethical issues and federal laws, that are recognized as contradictory, and that are likely to impact other centers across the country in their initial use of rapid WGS [9, 10]. Federal regulations for laboratory development of a new test require a research period prior to validation for clinical use, during which results are generated and precluded from return to patients and families. However, the research testing phase of rapid WGS raises an ethical challenge; namely, that results from rapid WGS could have immediately actionable findings. This brief report summarizes our center's approach to development of rapid WGS, navigating research development, laboratory certification requirements, and ethical challenges.

Regulatory Considerations

This project (Utah NeoSeq) was approved by the University of Utah Institutional Review Board (IRB). The development of rapid WGS was a collaboration between the University

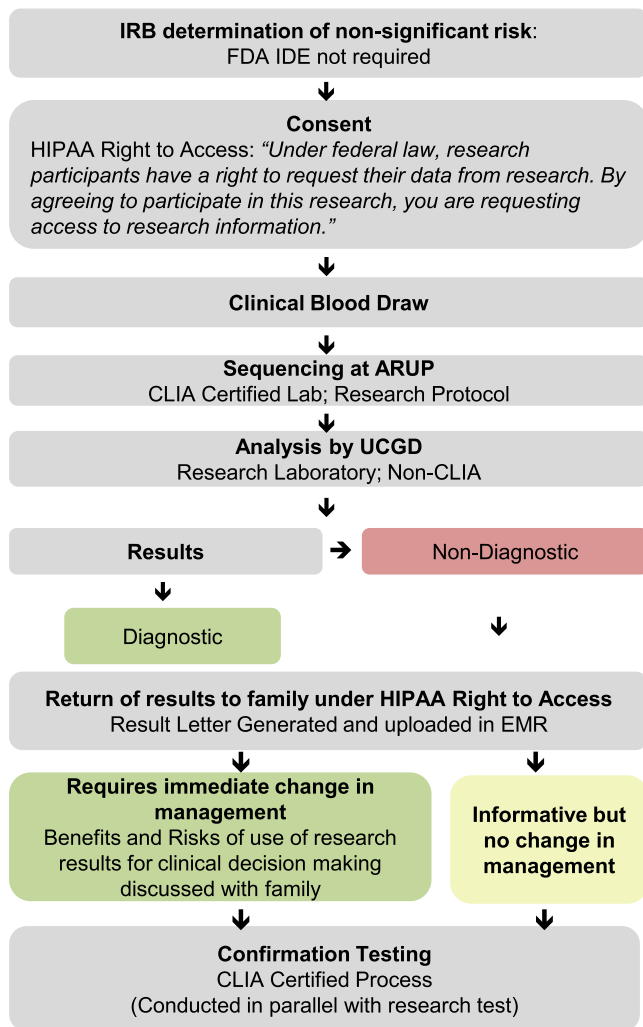


Fig. 1. Regulation considerations during research rapid WGS (NeoSeq). The NeoSeq consent contains language indicating HIPAA Right to Access and the parents' request to receive research results. The patient has a clinical blood draw and sequencing is done under a research protocol at ARUP Laboratories which is a CLIA certified lab. Analysis is done at a separate non-CLIA facility by the Utah Center for Genetic Discovery. All results are returned to the family by the study and clinical teams and the benefits and risks of a change in management are discussed. This testing is done in parallel with normal standard of care testing. Abbreviations: CLIA, Clinical Laboratory Improvement Amendments; EMR, electronic medical records; FDA, Food and Drug Administration; HIPAA, Health Insurance Portability and Accountability Act of 1996; IDE, Investigational Device Examination; IRB, institutional review board; UCGD, Utah Center for Genetic Discovery.

of Utah Department of Pediatrics, the Utah Center for Genetic Discovery, and ARUP Laboratories, a large reference laboratory (Fig. 1).

Patient access to genomic research results is governed by a complex set of regulatory bodies and associated laws and standards [10–13]. Initial discussions were in person between the study team and IRB committee. When the complex situation was recognized, we formed an expert panel of legal and ethical counsel, including members of the University of Utah IRB, University Office of General Counsel, bioethicists, genetic laboratory directors, and clinician researchers, with the goal of reviewing and evaluating applicable laws and weighing them with ethical considerations. We had a large in-person meeting then continued discussion by email. Here, we summarize the reviewed laws (Table 1) as they pertain to return of genomic research

results and discuss the application of these laws to our study protocols in the subsequent sections.

Bioethical Principles and Return of Results

Ethical considerations for implementing WGS in the NICU [14, 15] were a further consideration, given that as a research protocol there were competing interests of research result validity evaluation, and intervening in clinical care as quickly as possible. Although both interests strive to adhere to principles of beneficence, nonmaleficence, and autonomy, they can be at practical and regulatory odds. For example, if there is a gene variant (pyridoxine-dependent epilepsy) that causes on-going seizures, for which there is a low-risk treatment, a research result may allow clinicians to discuss possible treatment with parents, allowing them to adhere to all three of the above principles. However, acting on an “uncertified” result could be countered to those same principles. Withholding possible treatment would also be unethical if doing so harmed the patient. If research WGS identified a relevant gene variant, it would be difficult to obscure the result from the family because of the need for confirmatory testing. This would also create the potential for distrust, as the healthcare team would be aware of the research finding but would be precluded from sharing this with the family. We balanced these competing interests by developing a plan to return results centered around shared-decision making [16].

CLIA Regulations

The Clinical Laboratory Improvement Amendments (CLIA) are federal regulatory standards that guide clinical laboratory testing of human specimens. CLIA standards do not apply to research testing if results are not reported for diagnosis, prevention, treatment, or other health assessment purposes [12]. Prior to use in clinical patient care, an expectation is that a laboratory research and validate any new test, such as rapid WGS.

Recognition of the Health Insurance Portability and Accountability Act (HIPAA) Right to Results

The norm for our institution's informed consent process outlines a patient's right to obtain their protected health information (PHI) including genetic test results from a designated record set (DRS) under the HIPAA privacy rule. As the rapid WGS is performed under a research protocol, we recognized that returning results prior to a CLIA-certified confirmation is in tension with CLIA regulations. In an effort to resolve the tension between HIPAA and CLIA on this point, some academic research institutions have developed policies to exclude research results from the DRS.

The National Academies of Sciences evaluated these conflicting and ambiguous regulatory laws governing the return of individual results [10]. Their recommendations included better defining the DRS and requiring all HIPAA-covered entities completing human biospecimen research to have an IRB-approved plan for the return of results when requested under HIPAA. However, these issues and recommendations remain unresolved by regulatory agencies.

We therefore included in the informed consent the discussion of the benefits and risks of using research results for clinical care, and that there might be an in-depth discussion on this topic at the time of return of results. For the study child, we report variants related to their clinical presentation. We also will report variants of uncertain significance if associated with their medical issues. We do not report variants of unknown significance (VUS) that

Table 1. Federal regulatory laws governing return of Genomic research results

HIPAA	“Even if CLIA does not apply to the conduct of certain types of laboratory tests, HIPAA may still apply to require access to certain test reports to the extent the laboratory is a HIPAA covered entity and the information to which an individual is requesting access is protected health information under HIPAA” [11]
CLIA	CLIA does not apply to “components or functions of . . . research laboratories that test human specimens but do not report patient specific results for the diagnosis, prevention or treatment of any disease of impairment of, or the assessment of the health of individual patients” [12]
FDA	“Based on recent dialogue between FDA and SACHRP, it appears that FDA would require an entity (and a cognizant IRB) to determine if the research test poses significant risk or nonsignificant risk; this determination would depend in part on whether a confirmatory test in a CLIA laboratory is available or a comparable test does not exist, and the extent of risk in giving results to participants, even with caveats. If the research test poses a significant risk, then an IDE would need to be obtained before any results (with clinical interpretation) from that test could be returned to research subjects. FDA has also indicated that it may be permissible to provide ‘raw data’ to participants, without interpretation” [13]
Common Rule	“The Common Rule neither explicitly encourages nor explicitly prohibits the return of results to study participants, but require investigators to disclose their plans for returning individual research results (i.e., whether results will be returned to participants and, if so, under what conditions). If a research laboratory is (or is part of) a covered entity, participants may be told that their results will not be offered to them, as required by the revisions, even though they will retain a right to access the results under HIPAA if the results are part of the designated record set (DRS)” [10]

Abbreviations: CLIA, Clinical Laboratory Improvement Amendments; FDA, Food and Drug Administration; HIPAA, Health Insurance Portability and Accountability Act of 1996; IRB, institutional review board; SACHRP, Secretary’s Advisory Committee on Human Research Protections.

are not related to the clinical presentation. For the family members, we will report the presence or absence of variants that are detected in the study child. Optional results for the study child and family members include the American College of Medical Genetics 59 medically actionable incidental findings, which we report if the family opts in. (see our informed consent in the **Supplementary Information**). The results are returned to the family in person during a care conference by the study neonatologist, study medical geneticist, the attending neonatologist, and the attending medical geneticist. A research letter is also uploaded to the electronic medical record under the research tab. This allowed the research and clinical teams to utilize shared-decision making, whereby parents are engaged in NICU care decisions resulting in less decisional regret [16], with the goal to support parental autonomy and care provider obligation for beneficial care. The IRB would be contacted if there was a risk of harm to the patient from potential next steps guided by the research results.

Determination as a Nonsignificant Risk Device Study

Another important consideration was the determination that the proposed investigation would be considered a nonsignificant risk (NSR) device study. This requires approval of the protocol and compliance with NSR regulatory standards [17] but does not require submitting an Investigational Device Exemption (IDE) to the United States Food and Drug Administration (FDA).

This determination was based on a 2014 FDA decision regarding a comparable WGS study and the inclusion of appropriate risk-mitigating measures. In the 2014 precedent, the FDA had determined that the use of rapid WGS for critically ill neonates was a NSR study based on the following rationale: “1) Although you (the study) may return investigational test results to the treating physician that may influence important treatment decisions prior to their confirmation, this risk is lessened because the study population is critically ill, unlikely to be diagnosed quickly by other mechanisms, and suffers from a high mortality rate, 2) the treating physician can apply clinical judgment on whether treatment based on a preliminary, investigational result is warranted for a given patient, including considering the potential risk(s) the patient may incur given the nature/severity of the treatment, and 3) all returned investigational test results will ultimately be confirmed [18].”

There were two other factors in the NSR determination. First, the research rapid WGS used existing certified personnel and processes; including the hospital, laboratory, and staff involved. Second, the return of results and any clinical care decisions were managed by a joint team of specialists, including medical geneticists and neonatologists.

The high accuracy of WGS technology was also taken into consideration. WGS has a well-demonstrated record of clinically appropriate sensitivity and specificity [19], and the technology of Sanger sequencing used for CLIA confirmation is at a similar risk of errors as to WGS [20–22]. Therefore, rapid WGS technology itself was not a separate risk to consider for the study.

Discussion

NGS has the potential to transform care of critically ill infants in NICUs by providing early molecular diagnosis [5, 8, 23]. These benefits have accelerated efforts for clinical implementation of NGS such as rapid WGS. We describe a process that is of broad interest for the development of clinical rapid WGS, the balancing of laboratory certification requirements with ethical and HIPAA regulations. With advice from an expert panel of legal and ethical counsel, we created an IRB-approved protocol focused on informed consent, enabling clinical test validation to occur, in the setting of HIPAA right to access for families to ensure that medically actionable variants could be returned with the potential for clinical intervention.

The need for an approach to clinical development of rapid WGS arose because there are opposing regulations between laboratory testing validation requirements, HIPAA, and ethical considerations. Despite national committee recommendations [10], there are no accepted guidelines or regulations regarding the balance between the potential risks and errors of WGS completed in a research environment and the clinical need to act upon a rapid WGS result that may benefit a patient or significantly affect their outcome before results can be validated.

We concluded that honoring the HIPAA right to access PHI in the form of rapid WGS results was appropriate and ethically supported. The consensus of our expert panel was that withholding care in this situation would not be ethical. Considerations included sequencing being completed at a CLIA-certified laboratory, the

goal of the research (evaluating outcomes of rapid WGS), careful phenotype-driven analysis, and level of stress and uncertainty the families already are under.

Although it is possible for a scenario to occur where a WGS result is uncertain, but clinical intervention is of immediate concern and would require CLIA-based sequencing confirmation, this scenario is unlikely to occur in a fashion to impact patient care. This is because of the technical robustness of WGS, along with the low rate of results requiring clinical intervention in a time frame that would preclude CLIA-based sequencing or other orthogonal measures to demonstrate the validity of the WGS result.

In summary, with our collaborative approach, we defined a protocol that balances research standards and process with the potential clinical utility of a result. Our approach honors the Centers for Medicare and Medicaid Services' regulations governing CLIA certification of laboratory results before clinical intervention for the majority of nonurgent results. However, when the results are deemed critical for a prompt intervention by clinicians, our approach honors the right of parents under HIPAA to request results that are part of the DRS. This request is incorporated into the consent process. Continued research is needed in this area, including impacts on patients, families, and healthcare providers. We hope our described experience and research will provide a foundation for this process to be implemented at other institutions.

Supplementary Material. To view supplementary material for this article, please visit <https://doi.org/10.1017/cts.2021.833>.

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