An integrated end-to-end platform for engaged population-scale genomics

Cynthia L. Neben, Anjali D. Zimmer, Scott Topper, Alicia Y. Zhou
Color Genomics, Burlingame, CA

Introduction

Human subjects research is a partnership. It cannot begin without the generosity and trust of participants, and it will not be successful without researchers' attention focused on their scientific and clinical questions.

Participants expect to be acknowledged as interested parties as the project progresses. That interest can extend to study results, their personal data, clinically relevant incidental findings in that data, and derivative sample usage. Researchers recognize a duty to consider these expectations, but considerable logistical and ethical concerns exist. As large research institutions and national programs seek to integrate genomic information into the routine practice of medicine, a set of patterns has emerged. It is now evident that in order to support population-scale research, organizations need to address a long list of challenges. These include ensuring the analytical and clinical validity of generated data, providing tools for communication and education, managing data sharing and clinical routing, and constraining costs.

In contrast to diagnostic testing, which has been optimized to serve the 2% of the population that will need a rare disease diagnosis, population genomics programs require a different kind of infrastructure to deploy at scale. We have worked with over 100 organizations, including health systems, large research institutions, national programs, and employers, to offer scaled genomics-based programs using the Color Population Genomics Platform (PGP). Here we outline the core architectural elements that should be considered when implementing population genomics for research.

Program parameters

Table 1. Program decision matrix

Designing a population genomics platform presents a large number of decisions. Here we distill this to the most impactful choices that should be addressed first. Once addressed, these questions yield a relatively specific set of implications, based on which a program leadership team can move into an implementation phase.

Parameters	Primary Options
Program goals	• Recruitment • Data asset • Market differentiation • Value-based care
Laboratory infrastructure provider	• Build • Partner
Genomic data	• 30X WGS • Targeted panel + lcWGS
Clinical return of results	• CDC Tier 1 genomics applications[1] • ACMG Secondary Findings List[2] • PGx • Additional genes/conditions
Clinical services	• Genetic counseling • Pharmacy support • Variant classification • Report sign-out • Clinical services
Data integration	• EHR • Research data warehouse • Clinical data warehouse
Target population	• Unselected • High-risk • Affected • Ethnically diverse
Recruitment strategy	• Digital • Onsite • In-clinic
Data use permissions	• Clinical care • Population health management • Research and development

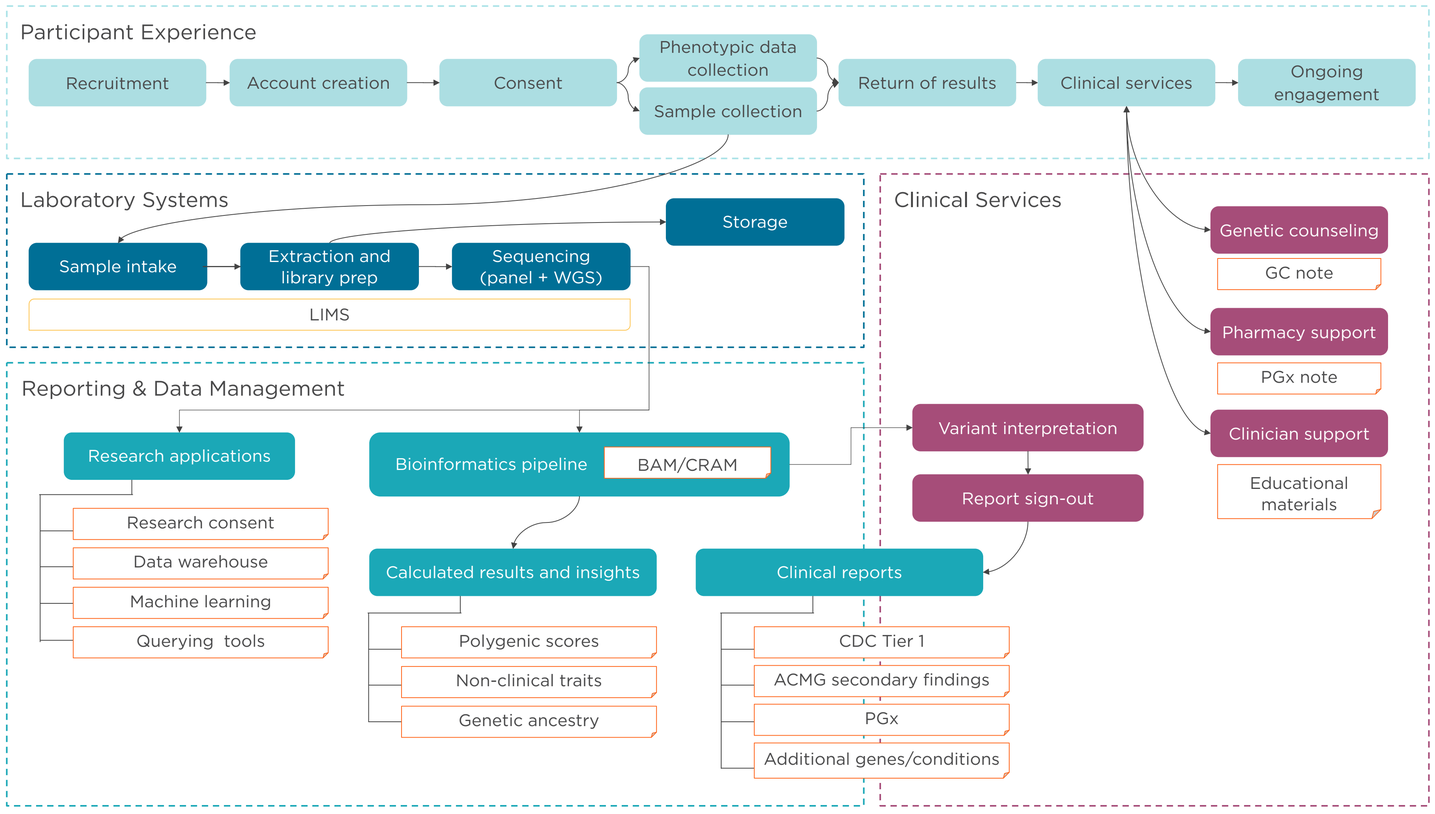
WGS, whole genome sequencing. lcWGS, low-coverage WGS. CDC, Center for Disease Control and Prevention. ACMG, American College of Medical Genetics and Genomics. PGx, pharmacogenomics. EHR, electronic health record.

Architecture overview

The architecture of the PGP supports end-to-end engaged population testing. Participants are engaged over the course of the study using digital tools such as customizable study-specific websites, consent and data gathering workflows, and online appointment scheduling. Integrated logistics support distributed sample collection and tracking. A state-of-the-art CLIA/CAP next-generation sequencing laboratory provides efficient and affordable data assets, including clinical, deep WGS, research-grade lcWGS, and customized analytics. Finally, the clinical infrastructure ensures that incidental findings are confirmed, clinically interpreted using best practices, and returned to participants and their healthcare provider using clear language, supported by Color's Genetic Counseling service.

Figure 1. Modular workflow

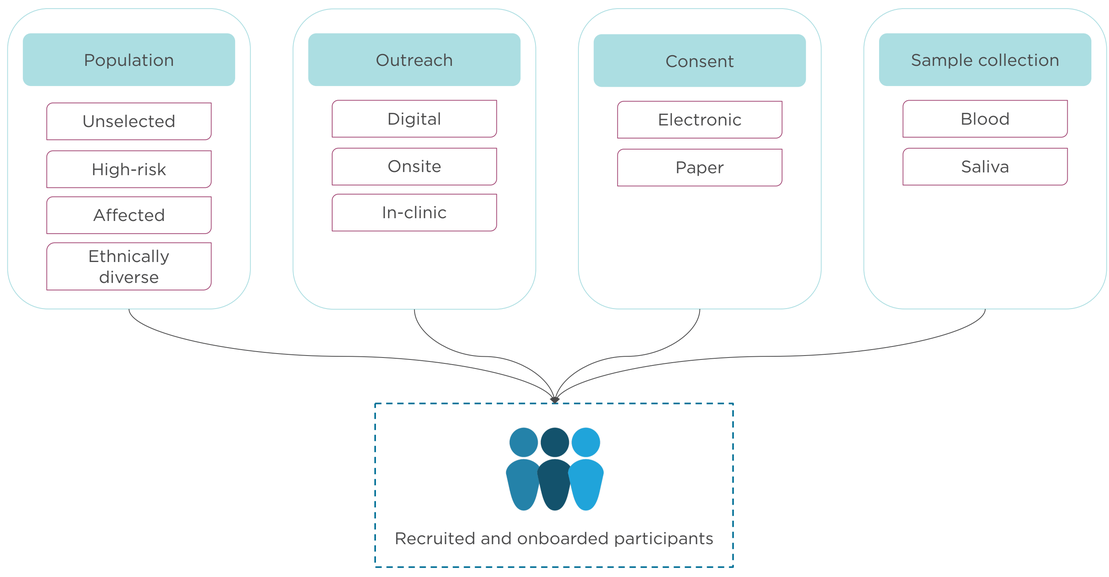
The PGP is comprised of three systems that support the participant experience: 1) laboratory systems, 2) reporting and data management, and 3) clinical services. All components must be integrated to provide a seamless experience for both participants and researchers.



Participant recruitment

Figure 2. Recruitment considerations

A key aspect of a successful population genomics initiative is effective recruitment of the right population. Considerations for population recruitment include population characteristics, outreach methodology, collection of informed consent, and specimen type. To note, informed consent should include information about who the study is being conducted by, why the research is being done, what will happen if participants join the study, what the risks/benefits of participating are, and who will have access to participants' information.



Discussion

- Returning genomics results to populations involves a great deal of complexity, but this complexity can be reduced to a few simple choices.
- Each program should not build every part of the genomics process from scratch. This "reinventing the wheel" approach leads to unnecessary costs, complexity, delays, and potential program instability.
- Programs should focus effort and risk on aspects that are most differentiating and most closely aligned with the fundamental program goals.
- Ethics and expectations have changed for genomics research, and it is now feasible and cost-effective to return results to research participants. Responsible genomics research should include return of results to all participants as a standard part of the research process due to the large potential health impact for every individual.

References

1. Tier 1 Genomics Applications and their Importance to Public Health | CDC. https://www.cdc.gov/genomics/implementation/toolkit/tier1.htm. Published January 28, 2019. Accessed February 4, 2019.

2. Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet Med.* 2017;19(2):249-255.