

GENOMES2PEOPLE: A ROADMAP FOR GENOMIC MEDICINE

Over the past few years, the role of genomics in the clinic has expanded enormously. At the forefront of this translational tsunami is the Genomes2People (G2P) Research Program. Founded by Robert Green, involving researchers from Brigham and Women's Hospital and Harvard Medical School, the playfully-named G2P is laying the groundwork for the future of genomic medicine.

"It's only been five years since the establishment of G2P, but the impact we've had on the genomics field through high-level publications and significant health outcomes data has been extremely exciting," says Robert Green.

"We are examining the integration of sequencing into the clinical care of adults and children, the impact of direct-to-consumer genetic testing, outcomes of genomic sequencing in healthy adults to gain insights into the potential future of personalised and preventative medicine, and much more."

Earlier in his career as a neurologist with a focus on Alzheimer's disease, Robert launched the REVEAL study – Risk Evaluation and Education for Alzheimer's Disease – a series of clinical trials exploring patient reactions to the knowledge of their genetic risk for Alzheimer's. Robert became so excited by the prospect of genomics that he took a leave from his position as a full professor of neurology and retrained in the Harvard Medical School Genetics Training Program, becoming board certified in medical genetics. He joined the Division of Genetics in the Department of Medicine at Brigham and Women's Hospital and Harvard Medical School in 2011.

"G2P started as a team of three individuals including Dr. Green and myself," explains Erin Drake, G2P's Director of Research Operations, "and has expanded to a team of nearly 20 innovative, engaged, and driven individuals including faculty, postdoctoral research fellows, genetic counsellors, project managers, research assistants, and student trainees."

G2P has a long reach, with a range of collaborators across healthcare, academia and industry. "G2P has built valuable relationships in translational genomics within our local community," says Erin, "specifically with the Broad Institute of MIT and Harvard, Partners HealthCare Personalized Medicine, the Partners HealthCare Laboratory of Molecular Medicine, and the Brigham Research Institute, to name a few."



"The relationships and collaborations we have formed, often with G2P serving as the central hub, have enabled us to accomplish so much more than we could on our own and really make for a rich and energising professional experience, environment and pace for G2P."

G2P's speciality is randomised clinical trials, many of them the first of their kind, designed to

lay the groundwork for what the future of precision medicine could look like, from top level studies like MedSeq, focussed on developing the framework for clinical use of genomic information, to examinations of direct-to-consumer genetic testing outcomes in the PGen Study.

"We anticipate a future in which genomic sequencing will be performed routinely, and a person's sequence will be available to all of their providers to guide medical care throughout the lifetime," adds Sarah Kalia, Director of Research Development and Genetic Counsellor at G2P.

"With the movement toward big data approaches in -omics research," she adds, "G2P envisions scaling up the impact of its expertise in clinical trial design and implementation, genomics policy, epidemiology, and the medical, behavioural and economic outcomes of disclosing genomic information."

Looking to the future of G2P's research, Robert says "G2P's strengths in clinical trial design and detailed clinical phenotyping, in collaboration with experts in big data, computation and data visualisation, could enable breakthroughs in scalable intermediate phenotyping to better characterise the role of genomic variation in health and disease."

Consumer genomics will also occupy the future work of G2P. "In the future, G2P plans to use smartphone apps that integrate with wearable tech for genomic risk stratification," says Robert. "We aim to create a computational disease risk algorithm that incorporates family health history, conduct multi -omics profiling, and utilise software and patient-facing apps to engage research participants."

"I can't wait to see what the next five years will bring for the field and for our program," adds Erin.



THE BABYSEQ PROJECT

Almost all infants born in the U.S. undergo routine newborn screening for approximately 30 different disorders using a simple heel stick blood test. The CDC (Centers for Disease Control and Prevention, in the U.S.) ranks this development in their Ten Great Public Health Achievements of the early 2000s, noting that newborn screening for certain endocrine disorders has led to earlier life-saving treatments and intervention for at least 3,400 additional babies every year.

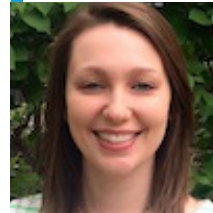
With the plunging costs and increasing scope of genome sequencing and other omics, many envision a future where the parents of newborns will have the opportunity to have their babies sequenced in the first days of life. However, the risks and benefits of genomic sequencing for newborns are not well-understood. This is where the BabySeq Project comes in. As Maggie Helm, Genetic Counsellor and Project Manager for BabySeq explains, “The BabySeq Project is a randomised, controlled trial through which we explore the medical, behavioural, and economic impact of newborn genomic sequencing.”

“We aim to evaluate the benefits and concerns for families and paediatricians receiving this information, assess parent and physician views, as well as understand the impact on healthcare decisions.”

Is it possible to integrate sequencing into the routine care of newborns, and can that information form a useful part of newborn care? Early pilot work conducted by this team showed that the vast majority – 82.7% – of parents surveyed would be somewhat, very or extremely interested in genomic screening for their healthy newborn. Recruitment for BabySeq began in early 2015.

The study, co-led by Robert and colleague Alan Beggs at Boston Children’s Hospital, is enrolling two groups of newborns, healthy and those admitted to neonatal intensive care, and randomly assigning each infant to either a sequencing group or a control. All will receive the standard newborn screening test, and the sequencing group will receive an additional whole exome sequence.

In addition to the immediate outcomes of sequencing, BabySeq will also look at the long-term medical impact of the information by monitoring participant health records and surveying families during a one-year period, collecting detailed information on their reactions to the study results, the impact they have on their family relationships and how useful the information they received was. Paediatricians will also be surveyed to assess medical utilisation of genomic sequencing information in newborns.

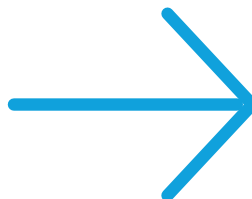


MAGGIE HELM, MS, CGC GENETIC COUNSELLOR AND PROJECT MANAGER FOR THE BABYSEQ PROJECT

“I have always had an interest in science, specifically genetics and genomics. Before going to graduate school for genetic counselling I worked in a lab making induced pluripotent stem (iPS) cells and then as a research assistant enrolling participants into a genetic biobank study. I began my career as a clinical genetic counsellor and realised I missed not participating in research. Then I joined the Genomes2People group. I have recently taken over the BabySeq Project, which I find to be a wonderful mix of my two passions – meeting with families and explaining complex genetic information, as well as being involved in cutting edge scientific research.”

“As the project manager and a genetic counsellor on this project I am involved in the day-to-day organisation of the study as well as consenting and disclosing results to families.”

“A major challenge in precision medicine is transition of genomics into the clinic, along with how much information should be returned and by whom. The BabySeq Project, as well as many other studies being performed by the G2P group, are aimed at understanding and answering these questions so that best practices can be discovered and followed in the translation of genomics into clinical care.





THE MEDSEQ PROJECT

Defining a process for integrating genome sequencing into standard clinical practice: this is the aim of the MedSeq Project. While that may sound straightforward on paper, it is one of the most critical challenges facing translational genomics.

"The goal of the MedSeq Project is to explore the medical, behavioural and economic outcomes of genomic medicine," explains Carrie Blout, MedSeq Project Manager and Genetic Counsellor. "We really want to investigate what it looks like when whole genome sequencing is brought to the clinic and provided to both healthy individuals and those who have a genetic condition."

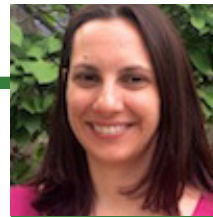
"At the beginning of the MedSeq Project, there was a basic question of 'how do we go from raw genomic sequencing data to a result we can give to non-geneticist physicians and their patients and put in the medical record?'" adds MedSeq Project co-investigator Joel Krier, "and what happens to everyone involved and the health system in general when we do that?"

"It was a novel paradigm, and not even the smartest and most experienced human geneticists in the room knew where we'd end up in the project. I think we collectively realised we needed to rely on fundamental principles of genetics/genomics and medical practice to guide us."

Patients are recruited to the study through their primary care physician or cardiologist. Jason Vassy, MedSeq co-investigator, primary care physician and Brigham and Women's Hospital and Harvard Medical School Instructor notes, "we're examining whether and how whole genome sequencing can enable disease prevention and improved healthcare in primary care and cardiology patients." The research group gathers data through patient and physician surveys, qualitative interviews, and review of audio-recorded and transcribed disclosure sessions.

The first phase of MedSeq has moved into its final funded year, with 200 patients across the two groups successfully recruited. Going forward Carrie anticipates that a key challenge for the project will be "assimilating all of the fantastic data the study has generated and working on getting it all published and out for the world to see and learn from."

"I feel the MedSeq Project, in addition to many of the other studies G2P is working on, really feels like the type of science that could impact future health care policy in this country."



CARRIE BLOUT, MS, CGC
GENETIC COUNSELLOR AND
PROJECT MANAGER FOR
THE MEDSEQ PROJECT

"I have always been fascinated by genetics and biology and when I learned genetic counselling it seemed like a perfect fit that would allow me to both work with people and to work in the field of genetics."

"A big challenge is to better understand penetrance. Thus far we have selected for patients who either themselves have symptoms or those who have a family history of a condition and that has informed how we interpret data. As more healthy individuals are tested, penetrance is a little less clear."



JOEL KRIER, MD, MMSC
INSTRUCTOR, BRIGHAM
AND WOMEN'S HOSPITAL,
HARVARD MEDICAL
SCHOOL

"In 2009-2010 I had the realisation that this technology and emerging field of genomics had the potential to completely change the way medicine is practiced over the course of my career. The timing and opportunity to train in medical genetics at a place like Harvard was irresistible, so I jumped in."

"I have had the opportunity to touch many parts of the MedSeq project, from sketching out the first draft of what became the "One-Page Genome Report" with Jason Vassy and Bill Lane (subsequently revised many times over!) to reading the transcripts of MD disclosures. I discovered I'm a molecular geneticist at heart (though I couldn't do a PCR to save my life), and that approach to thinking about genomics has had a big impact on how I approach questions in the clinical."



JASON VASSY, MD, MPH, SM
INSTRUCTOR, BRIGHAM AND WOMEN'S
HOSPITAL, HARVARD MEDICAL SCHOOL

"I am a primary care physician, and in that role I am always looking for effective approaches to improving the health of my patients."

"One of my primary roles has been liaison between cutting-edge genomic scientists and in-the-trenches primary care physicians, who often speak very different languages."

"Clinicians, health systems, and insurers will need evidence that precision medicine technologies improve patient outcomes before they support their use on a large scale. The challenge for the MedSeq Project and the field is to define and measure those outcomes."

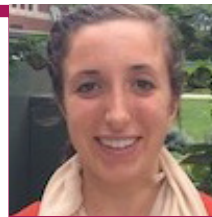
THE PGEN STUDY

The PGen Study is focussed on genetic testing in ostensibly healthy individuals through personal genetic testing (PGT), as it was practiced a few years ago when two DTC companies were selling health related genomic markers for common complex conditions.

"The PGen Study is examining the reactions and outcomes of customers who purchased DTC genetic testing from two companies between 2010-2013." says Erica Schonman, PGen Project Manager.

"The PGen Study has several goals: to describe who sought PGT and why; PGT's impact on their healthcare utilisation, as well as their risk perception and comprehension; and to assess what consumers do with genetic information in the domains of health behaviours, insurance changes, information seeking and communication with family members, health care providers, or other individuals."

The quantity of data gathered by the PGen Study is truly mind-boggling, with nearly two thousand participants having completed the series of surveys. This information is combined with genetic-risk information from each participant, provided with their permission by the partner companies.



ERICA SCHONMAN, MPH PROJECT MANAGER

"I've found my way into a scientific career through a life-long interest and passion for health equity and public health. Public health can take many shapes, and I'm excited to be working with Genomes2People on the forefront of translational genomics. In particular, I believe that the public health and genomics community is at an ideal time-point to evaluate approaches to integrating new genomic technologies/precision medicine into healthcare settings without aggravating existing disparities in healthcare. G2P has been, and continues to be, poised to make great strides investigating this area of public health."

"As Project Manager, I have the opportunity to coordinate the scientific efforts and help team members draft and polish manuscripts or other publications using PGen data so that we can disseminate findings from the study. We also get to dig deeper into the data to help identify meaningful stories and narratives that could influence future research and policy."

"As PGen wraps up, I'm better able to take the lessons and findings learned from that project and focus them towards the PeopleSeq Consortium, which I am now managing, and the broader field of precision medicine. I think one of the greatest challenges will be integrating genomics into clinical settings while considering the somewhat lacking levels of genomic literacy among both patients and providers. Limited knowledge and comprehension may hinder acceptance and appropriate integration of genomic technologies into healthcare settings. Yet, studies indicate interest in genomic technologies (and studies like PGen confirm this!) leaving wide open a perfect opportunity to incorporate genomic literacy efforts at all levels, from K-12, to community outreach, to professional continuing education."



Since 2011 G2P has grown from a team of three people to almost 20 individuals including faculty, postdoctoral research fellows, genetic counsellors, project managers, research assistants, and student trainees.





THE PEOPLESEQ CONSORTIUM

Much of the work around genomic sequencing has focussed on patients, people with diagnosed and undiagnosed conditions. But a growing number of physicians and clinicians are wondering what might be the potential benefits of genomic information to healthy people. Is there a benefit to sequencing individuals without symptoms? Given the increasing availability of whole genome sequencing to self-paying individuals, understanding the real benefits and potential harms of this information is now critical. Enter the PeopleSeq Consortium.

"The PeopleSeq Consortium aims to elucidate the medical, behavioural, and economic outcomes of genomic sequencing in ostensibly healthy adults who sought out sequencing from a non-medical source," says Daiva Nielsen, Postdoctoral Researcher. "While genomic sequencing has demonstrated benefit in clinical contexts for diagnosis/management of certain diseases, it is largely unknown if such information will be beneficial in presymptomatic, or asymptomatic individuals."

Within PeopleSeq are both research and commercial cohorts that return genomic sequence information to healthy people. These individuals are surveyed before and after receiving their results, to find out how the information impacts their lifestyle and healthcare behaviours. "The project will generate new knowledge to aid in our understanding of why individuals seek out sequencing... and what the medical and economic impacts for healthcare utilisation or potential healthcare savings will be", Daiva explains.

One of the big challenges facing PeopleSeq is the wide variety of genomic information given to patients in the study. As Daiva explains, "some cohorts provide information on genomics of ancestry while others do not, and some involve genetic counselling while others do not."

But, Daiva goes on, this variation is also a fascinating opportunity for the project. "This variation is representative of the true activities taking place in the field of non-medical genomic sequencing," she says, "and therefore our project is capturing an accurate picture of the current state of play."

"We are already thinking creatively of how we will embrace the diversity within our consortium, and we will use the most rigorous and innovative analytical approaches to answer our scientific questions."



DAIVA NIELSEN, PHD POSTDOCTORAL RESEARCHER

"I got involved in research studies as an undergraduate student and developed a strong interest in the scientific process. After completing my undergraduate degree, I enrolled in graduate studies and ultimately obtained my PhD in nutrigenomics – an area that considers how genetic variation impacts metabolism and response to nutrition, and how this may impact health. During the course of my doctoral studies, I read many of the publications that came out of the Genomes2People Research Program and I was intrigued to learn more about other aspects of genomics and contribute to the translational work being carried out by G2P. I am now a Canadian Institutes of Health Research-funded postdoctoral fellow working at G2P on the PeopleSeq Consortium, a large-scale longitudinal study examining the impacts of genomic sequencing in healthy adults. My scientific interests align with prevention and wellness, so the PeopleSeq Consortium was a fascinating project for me to become involved with."

"As a postdoctoral fellow, I am involved in the scientific direction of the PeopleSeq Consortium. I am actively involved in identifying cohorts to participate in our project, the development of our survey methodology, and creation of the specific research questions we pursue analytically. It has been a very rewarding experience to engage with such a dynamic group of cohorts and contribute to a project that will provide answers to many questions that are being asked in the field of genomics."

"The wider field of precision medicine faces a challenge that is essentially symbolised by the PeopleSeq Consortium. Individuals are independently able to obtain more and more information that may be relevant to their health. The entire field of medicine will need to adapt to these advances and embrace the fact that patients will be able to play a larger role in their healthcare decision-making. This is a very exciting time for patients and healthcare professionals."

REVEAL-SCAN™

THE REVEAL-SCAN STUDY

Before G2P there was REVEAL – Risk Evaluation and Education for Alzheimer’s Disease – funded by the NHGRI since 1999 to study how patients responded to finding out they were genetically pre-disposed to Alzheimer’s disease.

“Little was known at the time, though, about how individuals would respond to genetic test results,” remembers Kurt Christensen, “especially when they were healthy and did not have strong family histories of disease.”

“Would they understand the information they received? Would learning about genetic risks lead to anxiety and depression? Would testing motivate individuals to target lifestyle changes to reduce inherited risks? The REVEAL Study presented a rare opportunity to explore these questions with real, healthy patients receiving real test results, and has published over 30 manuscripts using this model as a paradigm for disclosure.”

REVEAL-SCAN – where SCAN stands for the Study of Communicating Amyloid Neuroimaging – was developed in response to the discovery of biomarkers for Alzheimer’s disease that can indicate an outwardly healthy person’s disease risk. As clinical trials push to recruit participants with certain AD biomarker profiles, REVEAL-SCAN seeks to find out whether prior knowledge of AD biomarkers changes how a cognitively normal person behaves in a clinical trial.

Still in its infancy, the project will begin recruiting participants this summer, seeking some 270 cognitively normal individuals who will all receive an amyloid brain scan. Only half of participants will receive their results, giving the research team a chance to assess how that knowledge impacts test behaviour.

“REVEAL-SCAN’s goal is to answer two critical questions,” says Project Manager Sheila Sutti. “Will individuals’ knowledge of their biomarker status bias cognitive outcomes? And will such knowledge prompt beneficial behaviour changes or cause adverse psychological and social consequences?”

“Answering these questions could change the way Alzheimer’s disease is screened, how we communicate to patients and providers, and provide meaningful insight on the validity and safety of AD clinical trials testing potential treatments in cognitively normal individuals with ‘preclinical AD.’”



KURT CHRISTENSEN, PHD, MPH
INSTRUCTOR, DEPARTMENT OF
MEDICINE

“In 2004, I enrolled in a special program in public health genomics at the University of Michigan School of Public Health with intentions to transition into a career in health promotion. I immediately knew I had found my calling. The program opened my eyes to the potential of genomics to revolutionise patient care and the practice of public health, especially through the early identification of inherited predispositions for chronic disease. I joined the third REVEAL Study trial in 2006 at its Michigan site, first as a site coordinator and then as a co-investigator; and I have continued to explore these questions in numerous Genomes2People projects, including REVEAL-SCAN.”

“The biggest challenge for REVEAL-SCAN will be to make the study as easy as possible for our participants. We are designing a protocol that meticulously collects high-quality data at multiple time points while being sensitive to the needs of a study population of older adults.”

“As far as the wider field of precision medicine is concerned, we are witnessing incredible advances in many fields, including genomics, proteomics, metabolomics, and the study of the microbiome. Presently, we are using each of these fields in isolation to improve people’s health. The true potential of precision medicine will be unlocked once we start to combine these data in an integrated approach.”



SHEILA SUTTI, MS, PROJECT MANAGER

“I always had an interest in neurogenetics, and, after getting my Bachelors of Science, I had the opportunity to further explore the field from a lab and research perspective through an NIH research training award program where I nurtured baby monkeys. As much as I loved my work there, I wanted to take on genetics from a different perspective that tied in both clinical and research aspects. I then entered into a genetic counselling program and quickly learned the significance of understanding the impact of genetic information in our society.” “Having trained in the Boston area, I was well aware of G2P and knew I wanted to join Dr Green’s team after graduating. Managing G2P’s genetics and Alzheimer’s disease portfolio seemed like the perfect fit for my interests in combining neurogenetics and clinical research.”

“Since we are gearing up to launch REVEAL-SCAN this summer, potential hurdles could be in participant recruitment and ensuring our population has a sufficient number of amyloid elevated scans and additional AD dementia risk factors for the planned analyses.

“In precision medicine, there exists a challenge in providing all information versus particular findings. As the demand for knowledge continues to grow, I see this obstacle continuously adapting and presenting itself with rapidly advancing genetic technologies and therapies.”

“In the era of genomic and precision medicine, I am so grateful to be part of such a dynamic team whose research answers the cutting-edge questions that will contribute to society’s medical, economical, behavioural and psychological knowledge and how we apply them.”