November 7, 2017

Last month, the genetics and genomics community assembled in Orlando, Florida for the 2017 American Society of Human Genetics Meeting. Of special note, Francis Collins and Bill Gates hosted a Facebook Live event at the meeting's Presidential Symposium, at which they discussed global health and genomics. I encourage you to check out that informative and entertaining discussion on YouTube.

Also last month, long-time NHGRI researcher Dr. Barbara Biesecker departed NHGRI and NIH to assume a senior research position at the Research Triangle Institute. Barb also stepped down as Director of the NHGRI-Johns Hopkins Genetic Counseling Training Program – a program that Barb founded roughly a quarter century ago! NHGRI will miss Barb, but we wish her all the best fortunes in her future endeavors.

This month's *The Genomics Landscape* features stories about:

- 40th Anniversary of Landmark DNA Sequencing Methods
- NHGRI's Dog Genome Project Engages on Reddit
- Thanksgiving: A Time for Turkey and Reflecting on Family Health History
- GA4GH Driver Projects: ClinGen & MatchMaker Exchange
- The Gene Doctors: A New Documentary Exploring Genetic Illnesses

All the best,

Watch here for current and upcoming locations of the Smithsonian-NHGRI exhibition "Genome: Unlocking Life's Code" as it tours North America!

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40th Anniversary of Landmark DNA Sequencing Methods

Forty years ago, a revolution in molecular biology and genetics began. In 1977, two landmark papers were published describing new readily implementable methods for DNA sequencing. Developed by Fred Sanger and Alan Coulson and Allan Maxam and Walter Gilbert, respectively, these methods began to infuse DNA sequencing throughout the broader biomedical research community and, a decade later, helped to spawn the beginning of the field of genomics.

DNA is the chemical that contains all the biological information for life. Determining the order of individual chemical bases (i.e., 'letters') in DNA, otherwise known as DNA sequencing, is essential to researchers interested in studying fundamental aspects of biology. As the 1970s marched along, better and better methods for isolating and manipulating DNA were becoming available. But before the two landmark 1977 publications, molecular biologists could only sequence small pieces of DNA at a time – greatly hindering molecular biology studies.

Sanger and Coulson developed the 'chain terminator' method, while Maxam and Gilbert developed the 'chemical cleavage' method. Both of these methods use distances along a DNA molecule from a radioactive label to position each base in a stretch of DNA. High-resolution gel electrophoresis was used to measure those distances, thereby allowing the order of all the bases to be inferred. In different ways, these methods began to lay a foundation for establishing approaches to perform high-throughput DNA sequencing. Ten years later, Lloyd Smith, Lee Hood, and Applied Biosystems developed automated machines that used the Sanger-based method with fluorescent rather than radioactive labels. These machines made the Human Genome Project – the successful effort to sequence all of the DNA in a human genome – possible.

Some fundamental aspects of these 1977 methods paved the way to the next pivotal point in the advancement of DNA sequencing, which occurred shortly after the Human Genome Project ended. By the mid-2000s, 'massively parallel' or 'next-generation' DNA sequencing (NGS) was all the rage in the genomics world. NGS approaches differ from the earlier methods by markedly increasing the number of DNA molecules being assessed at the same time.

The impact of NGS's arrival (and many other advances since) is readily evident by the historic drop in the cost of sequencing a human genome – approximately ~$1 billion by the HGP, ~$10 to $15 million in the mid-2000s, and currently ~$1,100, based on

NHGRI's Dog Genome Project Engages on Reddit

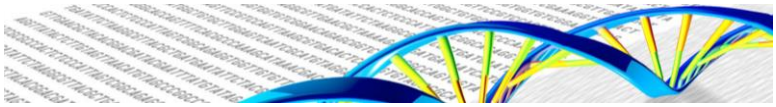
Researchers involved in NHGRI's Dog Genome Project are using canine genomics to better understand genomic variation in natural populations, as the 175 recognized dog breeds display astounding variation in phenotypic traits. Dogs can also be used as models for human diseases, as dogs exhibit many of the same diseases as humans. To highlight this work, Dr. Elaine Ostrander and members of her laboratory hosted a *Reddit Ask Me Anything* this month. The group addressed nearly 20 questions on topics ranging from what highly sought after breeds the project would like to sequence to the most recent common ancestor of domesticated dogs. To see the Q&A session, check out the Science Reddit page.

Thanksgiving: A Time for Turkey and Reflecting on Family Health History

My Family Health Portrait

This Thanksgiving, start a new tradition that could keep you and your family healthy. While gathering over turkey, collect your family health history. A tool called My Family Health Portrait, which is managed by NHGRI, can help by reminding you to enter your family health history and learn more about risk conditions that run in your family. Knowing your family health history can detect disease risks and help you to manage them before becoming sick – or to find the right diagnosis and treatment when you have a certain disease. To learn more about the importance of knowing your family health history and about research taking place at NHGRI on family health history, tune into our *Reddit Ask Me Anything* on Tuesday, November 21 at 1:00 p.m. ET with Dr. Laura Koehly and her research group. A recap will be posted after the event on genome.gov.

data generated by NHGRI's Genome Sequencing Program. NGS methods have been used to sequence the genomes of many organisms to understand their biology and evolution, and even to uncover important features of the human genome by comparison. These methods have also allowed for the sequencing of many thousands of human genomes to identify genes and other genomic elements associated with human health and disease. Many other applications of DNA sequencing have also been enabled, including: metagenomic sequencing, prenatal testing, forensics, pathogen outbreak monitoring, ancestry testing, and genetic testing.



As DNA sequencing has become faster and cheaper, the demand for it has increased substantially. One can now begin to imagine a future when biologists have representative genome-sequence information for all organisms on earth to aid their research studies. Human biologists might even have DNA- and RNA-sequence information for every cell in every tissue at every stage of life. Each person might have their genome sequence generated at birth, so that the information would be a helpful part of their healthcare throughout life.

The abundance of data generated by DNA sequencing has brought new challenges, though. Among them are issues associated with data storage, analysis, sharing, and security. Beyond the technical issues, there are equally complex questions about how DNA-sequence information is used across society and what it means in the context of cultures, communities, and self-identities. Going forward, researchers and policy makers will certainly have to address these (and many other issues) to fully deliver on the promises of genomics. Even so, a key to future advances is the imagination of creative thinkers who will apply DNA sequencing in novel ways to advance genomic knowledge and solve medical mysteries.

To commemorate the 40th anniversary of the two landmark 1977 publications on DNA sequencing methods, two papers were recently published in back-to-back issues of *Nature*. An outstanding review entitled "DNA sequencing at 40: past, present and future" was authored by Jay Shendure, Shankar Balasubramanian, George Church, Walter Gilbert, Jane Rogers, Jeffery Schloss, and Robert Waterston. Eric Green, Edward Rubin, and Maynard Olson co-authored the second paper, a commentary entitled "The future of DNA sequencing." These papers provide a deeper dive into the history of DNA sequencing and provide some thoughts about future applications. Together, these two papers provide a nice commemorative 'shout out' for the profound significance of the scientific pioneers who developed the 1977 methods for DNA sequencing.

GA4GH Driver Projects: ClinGen & MatchMaker Exchange

Global Alliance for Genomics & Health

The Global Alliance for Genomics and Health (GA4GH), an international organization whose mission is to create tools and standards for the responsible sharing of genomic and health data, has begun formal collaborations with multiple international initiatives as 2017 Driver Projects. Among this select group are ClinGen and Matchmaker Exchange. The goal of the NHGRI-funded ClinGen is to build an authoritative central resource that defines the clinical relevance of genes and genomic variants for use in precision medicine and research. The mission of Matchmaker Exchange is to facilitate genomic discovery through the exchange of phenotypic and genotypic profiles, NHGRI contributes to Matchmaker through the Centers for Mendelian Genomics Program. The GA4GH Driver Projects will help to identify, develop, and pilot data-sharing frameworks and standards in real settings, with the goal of ensuring that GA4GH's efforts are linked to the research and healthcare communities' most pressing needs.

The Gene Doctors: A New Documentary Exploring Genetic Illnesses

The Gene Doctors

A new documentary exploring genetic illnesses follows the journeys of patients and families living with diseases such as inherited blindness, cystic fibrosis, and muscular dystrophy. Entitled *The Gene Doctors*, the documentary also includes the stories of doctors and scientists who aim to establish the root causes of these diseases and embark on the new genomics frontier of medicine. *The Gene Doctors* will be broadcast on PBS television stations during November; a full listing of broadcast dates is available here. Beginning tomorrow, the documentary will also be available through Amazon Prime.

Spotlight on the All of Us Research Program

allofus.nih.gov

- Eric Dishman, Director of the *All of Us* Research Program, provides updates on the program in the *All of Us* Director's Corner.
  - Expanded Beta Phase: The first beta phase has been very successful. A second, expanded beta phase will start in early November.
  - Sharing Your Electronic Health Record (EHR): What's in your EHR and why are EHR data so valuable for researchers?

Genomics Research

DNA Damage Caused by Cancer Treatment Reversed by ZATT Protein

Gene Editing: Gold Nanoparticle Delivery Shows Promise

New Regions of the Human Genome Linked to Skin Color Variation in Some African Populations

Creative Minds: Using Machine Learning to Understand Genome Function

Scientists Find a Role for Parkinson's Gene in the Brain

Notable Accomplishments in Genomic Medicine

Funding News

NIH Operates Under a Continuing Resolution Through December 8, 2017

Application and Report Submission Flexibilities Available to Institutions Impacted by Hurricane Maria

Publication of the Revised NIH Grants Policy Statement

Statement on Article Publication Resulting from NIH Funded Research

New Videos

A Conversation with Bill Gates and Francis Collins on Global Health and Genomics at #ASHG17

The Gene Doctors: A New Film Exploring Genetic Illnesses

Integrating Genetics and Social Science: The Promises of Polygenic Scores - Jeremy Freese

NIH & NHGRI News

NIH-ACMG Fellowship in Genomic Medicine Program Management

GA4GH Strikes Formal Collaborations with 15 International Genomic Data Initiatives

Eric Hargan Named as Acting Secretary of the Department of Health and Human Services

Norman 'Ned' Sharpless Sworn in as Director of the National Cancer Institute

NIH Establishes New Research in Social Epigenomics to Address Health Disparities

NIH Awards to Test Ways to Store, Access, Share, and Compute on Biomedical Data in the Cloud

Unlocking Life's Code: October 2017 Newsletter