Biotechnology Discoveries and Applications

Extensions to high school science curriculum

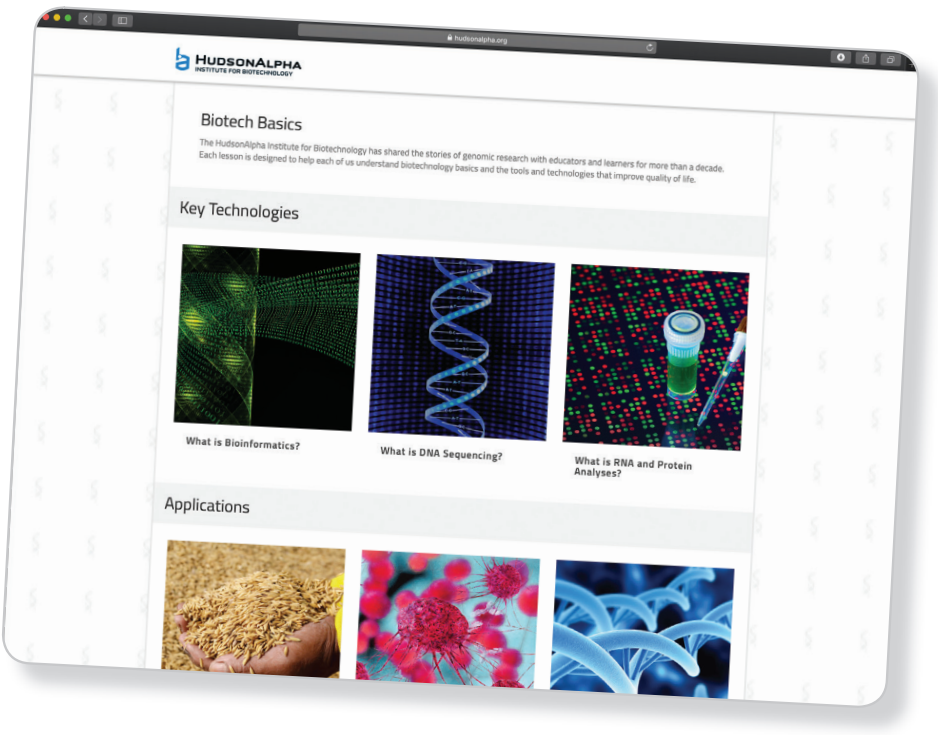
The 2019-2020 guidebook

HudsonAlpha
INSTITUTE FOR BIOTECHNOLOGY

2019-2020 GUIDEBOOK CONTENTS

ONLINE BIOTECH BASICS

Looking for a place to start? HudsonAlpha offers easy-to-understand explanations of foundational concepts at hudsonalpha.org/biotech-basics. Twenty-four key technologies or concepts are described in detail. Language and concepts are intentionally geared to a high school or public audience.



HudsonAlpha
INSTITUTE FOR BIOTECHNOLOGY

science for life®

About HudsonAlpha

The HudsonAlpha Institute for Biotechnology is a nonprofit institute dedicated to developing and applying scientific advances to health, agriculture, learning and commercialization. Opened in 2008, HudsonAlpha's vision is to leverage the synergy between discovery, education, medicine and economic development in genomic sciences to improve the human condition around the globe. The HudsonAlpha biotechnology campus consists of 152 acres nestled within Cummings Research Park, the nation's second largest research park. The state-of-the-art facilities co-locate nonprofit scientific researchers with entrepreneurs and educators. HudsonAlpha has become a national and international leader in genetics and genomics research and biotech education. It includes more than 35 diverse biotech companies on campus.

Genomic Research

HudsonAlpha scientists are adding to the world's body of knowledge about the basis of life, health, disease and biodiversity and seeking to enable:

- Earlier and/or less invasive diagnostics
- Better, more customized treatments for disease
- Improved food, fiber and energy sources

Significant Research Publications

Our researchers have been published in more than 700 scientific publications since the beginning of HudsonAlpha in 2008 to help secure a global leadership position in genomic research.

Current research focus areas are:

Basic Research
Foundational research aimed at improving scientific theories and understanding

Pediatrics
Undiagnosed childhood genetic disorders

Neurological and Psychiatric Disorders
including Alzheimer disease, Parkinson disease, ALS, Huntington disease, bipolar disorder, schizophrenia, autism and epilepsy

Cancer
Multiple forms of cancer, including breast, ovarian, prostate, kidney, brain, colon and pancreatic

Genomic Health
Leveraging the power of the human genome to diagnose, predict and prevent disease

Agriscience
Applying genomic knowledge to agriculture and bioenergy to create a more sustainable world

Immunogenomics
Application of genomic technology to understand the immune system's role in health and disease

Computational Biology and Bioinformatics
Deep computational analysis and interpretation of vast amounts of data, critical to the science of genomics

Global Footprint of Research Partnerships

HudsonAlpha partners with other research institutes and life sciences companies around the globe – and even in space – to make genomic discoveries.

Government support comes from:

National Science Foundation
Department of Energy
Joint Genome Institute
US Department of Agriculture
National Institutes of Health
National Human Genome Research Institute
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Heart, Lung and Brain Institute
National Institute of Mental Health
National Institute of Environmental Health Sciences

Educational Outreach

HudsonAlpha's Educational Programs

HudsonAlpha's Educational Outreach team inspires the next generation of life sciences researchers and workforce while building a more biotech-literate society. The dynamic educators at HudsonAlpha reach students, educators, medical providers, patients and the community through hands-on classroom modules, in-depth school and workshop experiences along with digital learning opportunities. HudsonAlpha also provides educational opportunities for healthcare providers and learning tools for patients who are making medical decisions using their personal genomic information. Additionally, the team builds genomics awareness through community outreach classes and events. During the 2018-2019 academic year, **1,266,514** individuals were impacted through HudsonAlpha Educational Outreach. Over the past decade, HudsonAlpha has reached nearly 5.5 million people with these programs.

Teacher Professional Learning

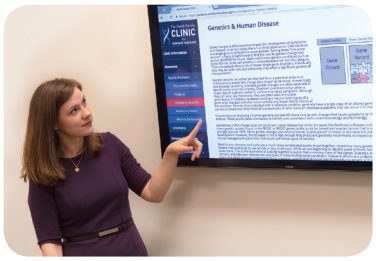
HudsonAlpha has several opportunities for teacher professional learning, ranging from single-day workshops to ongoing classroom support. These increase an educator's comfort in discussing genetic concepts and terminology along with the associated ethical, social and legal issues.

Student Experiences

Field trips, classroom visits by industry leaders, summer camp sessions, in-depth internship opportunities and college-level laboratory courses engage students in biotechnology-related fields, increase exposure to career options, provide mentoring opportunities and equip students with a toolbox of content-specific skills.

Classroom Kits and Digital Resources

HudsonAlpha has developed a module for seventh grade students matching state curriculum requirements related to DNA, how proteins are made and how genetic information is copied and segregated when cells divide. Multiple laboratory activities have also been crafted for students in grades 9-12. Activities highlight topics such as extracting DNA, exploring chromosome behavior in cells, diagnosing genetic disorders and using bioinformatics databases. Many of these resources are available to classrooms around the nation through a partnership with Carolina Biological (www.Carolina.com). HudsonAlpha has also crafted a suite of free digital activities available to students, educators and anyone who uses the Internet on a computer or mobile device.



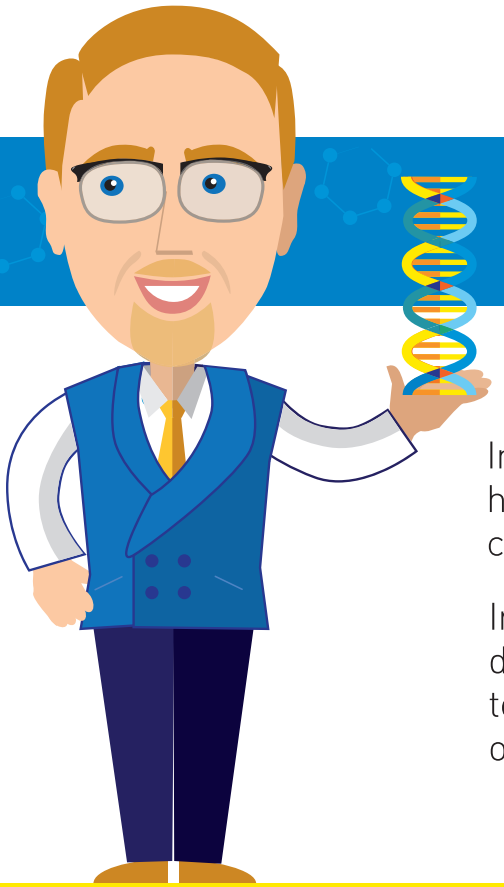
Clinical Applications

HudsonAlpha is empowering patients to be informed genomic healthcare consumers and members of society. Our genetic counselors are involved in providing patient education and support for clinical and research activities across the Institute. The genetic counseling team also provides education and training programs for healthcare providers and trainees to support the integration of genomics into routine and specialized medicine.

Biotech Enterprises

HudsonAlpha strengthens and diversifies Alabama's economy by fostering success in life sciences companies of all stages and sizes. Its 152-acre biotech campus within Cummings Research Park supports more than 35 tenant companies, from startups to global leaders, with space for more. HudsonAlpha offers turnkey and build-to-suit laboratory and office space for lease in an energizing environment with superior shared amenities. Bioscience enterprises on campus benefit from access to HudsonAlpha researchers as well as strategic support through investor forums, workforce and business assistance, marketing resources and bioscience networking events.

Dr. Neil Lamb's In Depth Science Blog



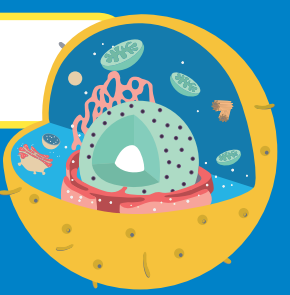
shareable science

In a field that pushes the boundaries of human discovery daily, keeping the conversation current matters a great deal.

In the Shareable Science blog, Dr. Lamb breaks down topics that show up everywhere from television news shows to the watercoolers of research institutes.

If you want to see how genomics plays out everywhere from grocery aisles to crime scenes, Shareable Science can help bring topics too small to see with the human eye into realms too big to ignore. Check back regularly for new content and engage your mind with the same questions that captivate some of the world's leading scientists.

www.shareable-science.org



Professional Learning for Life Science Educators

GTAC® National

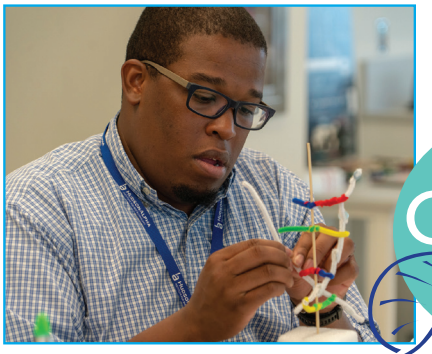
For National Educators

GTAC: National is a five-day professional learning academy that prepares life science educators to address high school level genetics, genomics and biotech content in their classrooms. Take a deep dive into topics such as cancer and clinical genomics, common complex diseases and agricultural genomics. Our experienced education team will also provide guidance for using free HudsonAlpha digital resources such as iCell, videos, online modules and a lesson plan library. Participation will also include 40 hours of professional learning credit and HudsonAlpha-developed kits and classroom materials.

hudsonalpha.org/GTACnational

For Alabama Educators

Alabama teachers, we've got programs available just for you. **To learn more about GTAC: Essential Biology & GTAC: Advanced Concepts, visit hudsonalpha.org/GTAC.**



GTAC® Essential Biology

GTAC® Advanced Concepts

HudsonAlpha
INSTITUTE FOR BIOTECHNOLOGY

EXECUTIVE SUMMARY

Do you remember the first time you heard about DNA?

For our Baby Boomer and Gen-X readers, I imagine the term first surfaced as part of a lecture in a middle or high school biology classroom. It might have been linked to a discussion about Mendel's pea plants or perhaps a lesson on cell structure.

How times have changed! Today's learners encounter DNA through storylines in TV shows and movies, commercials for ancestry profiles and other direct-to-consumer testing, news stories about major developments and even a Spotify playlist "tailored to your DNA." As a science educator, part of me rejoices that genetics has become such a ubiquitous part of our culture. However, I recognize that most of these references fail to communicate the nuances of the science, contributing to major misconceptions. Today's students may step into the classroom knowing more about genetics than any prior generation but understanding it less.

Savvy educators use this as a powerful teaching opportunity, engaging students with examples gathered from the world around them. Here at HudsonAlpha, we applaud that approach. It's one of the key objectives for our annual Guidebook — placing current DNA findings at a teacher's fingertips.

It's been quite the year for genome-related news, and this edition of the Guidebook is packed with nearly four dozen stories, drawn from research published between August 1, 2018 and July 31, 2019.

Some of the stories I find especially intriguing:

- a proof-of-concept approach to turn yeast into solar-powered micro-factories *(pg. 8)*
- the head spinning explanation of how a set of semi-identical twins came into being *(pg. 9)*
- the firestorm of controversy that erupted around the announcement of gene-edited babies *(pg. 11)*
- gene and cell-based therapies that offer patients seemingly miraculous treatments, but come with enormous price tags *(pg. 12)*
- the opportunity and challenge of polygenic risk scores *(pg.13)*
- how sleep gives our cells a chance to repair DNA damage *(pg. 15)*
- the widespread use of the first gene-edited food product—a "healthier" soybean oil *(pg. 16)*
- for our cat-loving readers, a crowd-funded sequencing of internet kitty sensation Lil BUB *(pg. 7)*

Neil Lamb, PhD
Vice President for Educational Outreach
HudsonAlpha Institute for Biotechnology

If you're a long-term reader of the Guidebook, you'll note that this edition is significantly shorter in length. The 24 foundational stories traditionally found in the back half of the Guidebook have a new home online at hudsonalpha.org/biotech-basics. While retaining their easy-to-understand format, they are now accessible in a more environmentally friendly format.

This year's Guidebook would not have been possible without the exceptional talents of David Kumbroch, Madelene Loftin, Leigha Parker and Cathleen Shaw. It is an honor to count them as colleagues, and I am thankful for their assistance in developing, designing and assembling these pages.

Happy reading!

Neil E. Lamb, Ph.D.

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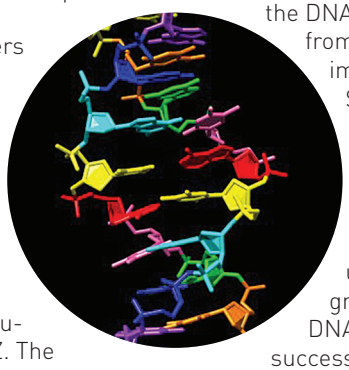
SCIENCE SNAPSHOTS

a quick rundown of 10 genetics and biotech stories

1. Across the animal kingdom, mitochondria and mitochondrial DNA are generally inherited only from the mother. Surprisingly, DNA sequencing data identified three unrelated families where mitochondrial DNA was inherited from both parents. The scientists who led this study suggest these rare paternal mtDNA transmissions may result from mutations in genes that typically eliminate the father's mtDNA from sperm and fertilized embryos. Other researchers have failed to replicate these findings, and the claims of mtDNA biparental inheritance await further validation.

2. Researchers have sequenced the genome of two key varieties of domesticated wheat: durum wheat, used to make pasta, and a bread wheat variety called Chinese Spring. Wheat, the world's most widely cultivated crop, has a particularly complex genome — five times larger than that of a human and comprised of multiple sub-genomes. To further complicate the analysis, over three-quarters of the genome contains repeated sequences. More than 107,000 genes were identified, spread across 21 chromosomes.

3. A growing number of companies are placing a canine spin on DNA profiling, hoping to solve pet waste problems. Surveys suggest as many as 40 percent of dog owners don't pick up after their pets. That can be especially problematic for property managers in high-density housing units. Owners swab the inside of their pet's cheek and submit the sample to the testing company, who generates a DNA profile and enters the dog into their registry. Un-scooped feeces are then tested against the registry in an attempt to identify the canine "poo-petrator."



4. Scientists recently expanded the library of DNA nucleotides from A, T, C, and G to include B, S, P and Z. The four new nucleotides were crafted in a laboratory but integrate into the double helix without disrupting its structure. Researchers call their expanded genetic alphabet hachimoji - which means "eight letter" in Japanese. The synthetic nucleotides can pair: B with S, P with Z and can be transcribed into RNA. Scientists have long dreamed of ways to create customized proteins that execute a specialized task. Having twice as many genetic building blocks at their disposal could significantly improve the design options for tailor-made biological based drugs and therapies. Hachimoji could also find use as a storage tool for safely encoding information long-term.

More details can be found in the Shareable Science blogpost: Scientists showcase hachimoji, an expanded genetic language

5. Lil BUB is a cat with 2.3 million Instagram® followers and nearly 3 million Facebook® fans. She was born with a number of genetic anomalies, including extra toes, no teeth, enormous green eyes, a feline form of dwarfism and a bone-hardening disorder called osteoporosis. Following a crowdfunding effort, the genome of Lil BUB has been sequenced, yielding insight about her features. She carries a mutation in the Sonic hedgehog gene, which explains her extra toes (a genetic change also found in Hemingway cats). Her other features are due to two copies of a frameshift mutation in a gene associated with bone formation. This mutation causes bone to harden too quickly, stunting growth and leading to Lil BUB's unusual features.

6. Researchers have pinpointed a previously unknown cause of epilepsy in infants, hidden in a gene called *SCN1A*. The mutation incorporates a damaging piece of genetic code, called a poison exon, into the final instructions for the SCN1A protein. The poison exon prematurely cancels the protein's production and leads to the seizure disorder by disrupting neural function. Other studies have identified the presence of hundreds of similar poison exons across the genome, suggesting this mechanism may be a component of other human diseases.

The laboratories of HudsonAlpha faculty researchers Greg Barsh MD, PhD, Rick Myers PhD, and Greg Cooper PhD contributed to this research.

7. Cruciferous vegetables like Brussels sprouts, broccoli and kale contain a molecule that silences a gene known for its role in tumor formation. Indole-3-carbinol silences the *WWP1* gene, restoring the cell's ability to activate tumor suppression pathways. There's a catch, however - over five pounds of raw Brussels sprouts would need to be eaten every day to maximize the anti-cancer effect.

8. Four high school students from Minnesota won the 2018 Genes in Space competition with their idea for simulating the DNA damaging effects of cosmic radiation using CRISPR. The students designed a CRISPR Cas9 system that made targeted changes in the DNA of yeast cells. Following further development help from Boeing, MiniPCR and NASA, the student's experiment launched in early 2019. International Space Station (ISS) astronauts performed the experiment to investigate DNA repair efficiency in microgravity. After the CRISPR damage, cells were monitored using PCR and sequencing-based tests to measure how effectively DNA repair mechanisms dealt with the injury. This experiment marks the first use of CRISPR in space. The entire investigation; growing yeast cells, inducing DNA lesions, PCR and DNA sequencing took place on the space station. The success of the experiment provides further evidence that terrestrial genomic tools are viable in space.

9. Thanks to their antlers, deer qualify as the only mammal that can regrow lost body parts. Unlike horns (which are made of keratin and remain attached to an animal), antlers are made of bone and shed and regrow annually. Antler development is influenced by nutrition, habitat and genetics. Scientists have identified two genes, *Uhrf1* and *s100a10*, that work in tandem to control antler development in red deer. *Uhrf1* promotes cell division and growth and *s100a10* regulates the rapid hardening (calcification) of the antlers. Because these same genes are also present in humans, understanding bone growth in deer may shed light on treatments for bone diseases and fractures.

10. While conventional wisdom says the womb is a sterile place, free from bacteria, recent studies provide conflicting answers. Amniotic fluid was collected from 43 pregnant women giving birth by cesarean section. The next day, first-pass meconium (an infant's first poop) was collected from the newborns. Researchers found bacterial DNA in nearly all the samples, even after controlling for potential contamination from laboratory surfaces and reagents. In contrast, a study of more than 500 placentas found that only about five percent of the samples truly contained bacteria - and those were colonized with only a single type of Streptococcus.

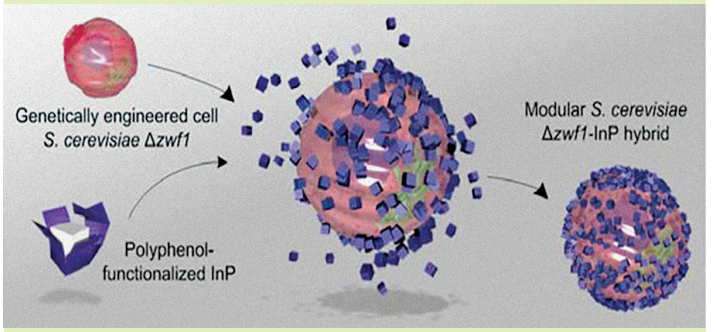
NEW FINDINGS

Tiny solar panels used to make yeast into more efficient drug factories

Scientists have successfully attached light-harvesting nanoparticles to yeast cells in order to ramp up the cell's ability to build complex macromolecules. The nanoparticles function as tiny solar panels, allowing the yeast to convert solar energy into carbon bonds.

S. cerevisiae, or brewer's yeast, has been well-characterized by scientists and is frequently genetically engineered to convert simple sugars into helpful drugs and compounds. A series of enzymatic reactions breaks the existing chemical bonds, modifying the molecular structure in a step-by-step process to produce the finished product.

Nicotinamide adenine dinucleotide phosphate (NADP) is an important energy-carrying helper in this molecular renovation. It accepts electrons and hydrogen atoms to form NADPH, which it then donates to power the enzymes involved in the molecular remodeling. After donating these chemical building blocks, the NADP acquires an additional electron and hydrogen atom, donating those as well at a later stage of construction. This cycle of "gain and donate" is critical to successfully assembling the growing molecule.



Scientists were looking for ways to boost the availability of energy that NADP shuttles to the construction site. They coated the yeast with nanoparticles of indium phosphide, a common component of solar panels. For this experiment, they worked with yeast genetically engineered to produce shikimic acid, an early building block of various medications. When exposed to white light, the nanoparticles capture electrons from the light and donate them to NADP, providing a plentiful energy source. This allows the chemical construction process to proceed more quickly — the yeast tripled and even quadrupled their production of shikimic acid.

Researchers believe this same energy-capture approach could be used to assemble other, more complex macromolecules, turning yeast into solar-powered chemical production powerhouses.

REFERENCE: Guo J. et al. Light-driven fine chemical production in yeast biohybrids. Science (2018) 362:813-16 doi: 10.1126/science.aat9777.

Poverty leaves a lasting genetic impact

Adding more complications to the balance of nature versus nurture, scientists published research in April 2019 demonstrating that poverty creates a lasting genetic impact in individuals. The study suggested that socioeconomic status can become embedded across wide swathes of the genome by impacting levels of DNA methylation.

DNA methylation is part of the epigenetic process that determines the degree to which certain genes are expressed. Genes are often described as being on or off, but they are less like flip switches and more like dimmer switches. The level of activation or silencing can matter a great deal in ensuring that a gene does its job correctly. DNA methylation is one of the factors that adjusts that dimmer switch.

This study found poverty-linked changes in methylation at 2,500 sites across 1,500 genes. It's important to note that the biological impact of poverty-linked methylation is unknown. Further research is required to determine the functional consequence of methylation changes at these sites.

Health studies have frequently linked socioeconomic status to long-term health outcomes, even when that socioeconomic status is not a factor at the time of the health issue. It is not understood what mechanisms translate the experiences of poverty into long-term medical issues, but altering DNA methylation may be a critical pathway.

Understanding how changing methylation across these 2,500 genetic loci impacts health outcomes could reveal key factors in how socioeconomic status influences human health, even long after that status changes.

REFERENCE: McDade T.W. et al. Genome-wide analysis of DNA methylation in relation tosocioeconomic status during development and early adulthood. American Journal of Physical Anthropology (2019) 169:3-11 doi: 10.1002/ajpa.23800.

Morphing from female to male

While gender is a fixed trait for most organisms, some plants and animals can switch genders in response to specific environmental cues. Consider the bluehead wrasse — a small Caribbean coral reef fish. When the dominant male is removed from his harem of females, the largest female rapidly undergoes a gender transition. Within minutes, she becomes aggressive and establishes social dominance over the other females. Her coloration changes within hours and in little more than a week, her ovaries transform into sperm-producing testes.

Scientists have recently uncovered the molecular regulators of this remarkable change. They believe the reversal is triggered by visual cues indicating the male's absence. Levels of the stress hormone cortisol increase, activating brain neurotransmitters linked to territoriality and aggression and initiating the cellular machinery that reprograms ovaries into testes. Changes in DNA methylation silence genes associated with estrogen production and ovary maintenance. This is followed by the activation of genes that increase androgen levels, regulate testicular development and drive masculinization. This research identifies how an environmental factor (absence of the dominant male) triggers a major shift in DNA methylation, altering gene expression and leading to both behavioral and cellular reprogramming.

REFERENCE: Todd E.V. et al. Stress, novel sex genes, and epigenetic reprogramming orchestrate socially controlled sex change. Science Advances (2019) 5:eaaw7006 doi: 10.1126/sciadv.aaw7006.

What makes nice foxes nice?

One of the most robust dog domestication studies in the world actually focuses on foxes. Russian researchers have run a farm breeding foxes based on their aggression levels for more than sixty years, hoping to reveal some of the genetic mechanisms of domestication. Now scientists the world over have a new tool for interpreting the data. In August 2018, researchers published a reference genome for foxes, giving scientists a starting point for comparison. They also sequenced the genomes of twenty foxes from the Russian experiment — ten each from the aggressive and non-aggressive groups.

This dataset represents a huge step forward in understanding the genetic components behind the shifts in behavior and physical appearance associated with fox domestication, potentially revealing secrets of behavior from all corners of the animal kingdom.

For example, the aggressive and non-aggressive groups of foxes carried different versions of the *SorCS1* gene, which had not previously been linked to social behavior. However, *SorCS1* has been associated with Alzheimer disease and autism in humans. Mouse studies show that it's involved in synapse formation and neuronal function.

Another region of interest, one linked to Williams-Beuren syndrome, showed up in aggressive foxes but not the others, defying expectations. People with Williams-Beuren syndrome are known to be exceptionally friendly, so it was theorized that the region might help with domestication. The syndrome in people is also linked to anxiety, which could explain why it triggers an aggression response in the foxes.

This fresh toolset opens up new avenues and illuminates just how long the path is to truly understanding the genetic process of domestication.

REFERENCE: Kukekova, A.V.. et al. Red fox genome assembly identifies genomic regions associated with tame and aggressive behaviours. Nature Ecology and Evolution (2018) 2:1479-91 doi: 10.1038/s41559-018-0611-6.

Auburn University Assistant Professor and HudsonAlpha adjunct faculty member Xu Wang, PhD contributed to this work.

Semi-identical twins

Researchers reported on a twin pregnancy with a shared placenta (suggesting identical twins), but different genders (implying fraternal instead). Genetic testing showed the twins share all their maternal DNA but only 78% of their paternal DNA. This form of semi-identical, or sesquizygotic twinning is believed to occur when two sperm (call them S1 & S2) simultaneously fertilize a single egg (E). These embryos don't usually survive to birth, but scientists hypothesize that this embryo divided the three sets of chromosomes (E, S1, S2) into three cell types: ES1, ES2 and S1S2. With no maternal contribution, the S1S2 cells didn't develop. The embryo then split to produce the twins, each with a different proportion of ES1 and ES2 cells. It appears that one sperm carried an X chromosome and the other contained a Y. The male twin has approximately even percentages of XX and XY cells, while 90% of the cells tested from the female twin are XX.

REFERENCES: A video from the New England Journal of Medicine that explains sesquizygosity can be found at https://www.youtube.com/watch?v=06_nsL46rEY.

Gabbett M.T. et al. Molecular Support for Heterogonesis Resulting in Sesquizygotic Twinning. New England Journal of Medicine (2019) 380:842-9 doi: 10.1056/NEJMoa1701313.

NEW FINDINGS

Sharing research profits with customers

The consumer genetics market continues to boom, in part because of affordable sequencing costs and public interest, but also because the data generated helps to fuel both public and private research. Some groups are looking to give people more control over how their genomic data gets used while cutting them in on the profits from research.

Both academic and pharmaceutical research rely on diverse sets of de-identified genomic data. Direct-to-consumer genetics companies can offer that kind of data to these research organizations. Many companies offer people information about their genome and affordable testing in exchange for the ability to use the information, but now some companies are converting customers into a kind of partner.

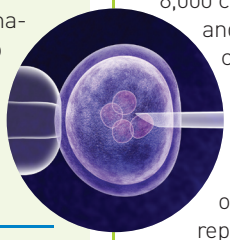
For example, LunaDNA lets users store genetic records on the LunaDNA platform. When researchers buy those records, that individual is given shares in LunaDNA. The model ultimately results in profit-sharing. Encrypgen takes a different approach, letting researchers use their platform to purchase de-identified genomic profiles directly from users with a cryptocurrency called DNA Tokens. Both approaches give the consumer greater agency over the availability of his or her data as well as a more direct interest in money made from their genetic information.

More details can be found in the Shareable Science blogpost: Making coin off your genome

Switching embryo genes on

When an egg is fertilized by a sperm, the resulting zygote rapidly undergoes many rounds of cell division to produce a ball-shaped mass of cells. These divisions are regulated by a set of maternal enzymes and other proteins pre-loaded into the egg. The genome of the zygote is silent during this initial stage. Ultimately the genome "awakens" and activates transcription from thousands of genes to continue embryonic development. Until recently, the mechanism behind zygotic genome activation (ZGA) was a mystery. By studying gene activity across individual cells within frog embryos, researchers have now determined cell size is the defining feature of ZGA.

During early development, the zygote undergoes cell division but the cells don't grow in size. Every round reduces the cell's volume, increasing the ratio of DNA to cytoplasm. At the 4,000–8,000 cell stage, the frog embryo contains a range of cell sizes, and the smallest cells begin activating their genome. As cell division continues, ZGA initiates across the remainder of the embryo when cell diameter drops below 45 micrometers (roughly equal to about half the width of a strand of hair). This finding suggests a model where the egg contains a high concentration of repressors of transcription. As the zygote divides, the number of repressors present in each cell drops. Ultimately the level of repressors falls below some threshold, releasing the block on transcription and activating the zygotic genome.



REFERENCE: Chen H. et al. Spatiotemporal Patterning of Zygotic Genome Activation in a Model Vertebrate Embryo. Developmental Cell (2019) 49:852-66 doi: 10.1016/j.devcel.2019.05.036.

Study finds fecal transplants cut autism symptoms nearly in half

While behavioral therapies and psychiatric medications can address some of the symptoms that fall under Autism spectrum disorder (ASD), scientists search for ways to effectively treat core symptoms like difficulty with communication, restricted interests and repetitive behaviors. A two-year study links fecal microbiota transplantation to a major reduction in those symptoms.

Scientists had previously compared the gut microbiome of children with autism to the microbiome of children that develop typically. Those with autism had lower diversity and were missing some types of helpful bacteria. The researchers developed a treatment plan they hoped would alter the gut microbiome of the children with autism. Treatment took place over ten weeks, including a pre-treatment with a bowel cleanse and stomach acid suppressant, followed by seven to eight weeks of daily fecal microbiota transfer.

The initial study analyzed the children eight weeks after therapy ended. The treatment increased microbial diversity and parents reported slow but consistent improvement in their child's ASD symptoms. This follow-up paper found the diversity and behavioral gains remain at the two year post-treatment mark. A professional evaluator concluded the children with autism experienced a 45% reduction in core symptoms related to language, social interaction and behavior.

Larger clinical trials are required before this type of therapy can be widely considered, but these findings significantly add to a growing body of evidence that gut microbial composition is a modifiable influencer of behavior.

More details can be found in the Shareable Science blogpost: Autism linked to gut bacteria in new study

REFERENCE: Kang D-W. et al. Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota. Scientific Reports (2019) 9:5821 doi: 10.1038/s41598-019-42183-0.

Humans gained viral resistances from interbreeding with Neanderthals

As *Homo sapiens* migrated out of Africa into Europe, they encountered a number of new threats to their survival — from a different climate to new diseases. They also encountered Neanderthals, an earlier version of humans that had already adapted to these challenges.

A study published in late 2018 illustrates that through interbreeding with Neanderthals, *Homo sapiens* gained important genetic resistance to infection by a number of viruses. The paper explains that it would have taken *Homo sapiens* quite some time to develop the genetic resistances on their own, and it was much faster to "borrow" the resistances from interbreeding with Neanderthals.

Researchers found 152 examples of genes that encode virus-interacting proteins in modern humans that originated in Neanderthals. These genes specifically help humans resist viruses made from RNA. Common examples of RNA viruses include influenza, hepatitis C and HIV. The number of genes combined with the length of preserved sequences suggests that they conferred an evolutionary advantage.

REFERENCE: Enard D. and Petrov D.A. Evidence that RNA Viruses Drove Adaptive Introgression between Neanderthals and Modern Humans. Cell (2019) 175:360-71 doi: 10.1016/j.cell.2018.08.034.

Bacteria convert type A blood into universal donor

Researchers have successfully used genes from human gut bacteria to convert type A blood into type O, which is known as the universal donor because it is compatible for transfusion with all other blood types.

The blood types: A, B, AB and O are defined by sugar molecules on the surface of the red blood cells which typically make them incompatible with one another. These molecules, or blood antigens, trigger a massive immune response if they are put into the body of someone with another blood type. Type O blood lacks those blood antigens, meaning it is compatible with the other types.

Type O blood is incredibly valuable in the medical world, both because it helps protect against blood shortages and because it can be deployed quickly in an emergency situation where you don't have time to determine a patient's blood type.

To convert the type A blood, researchers collected DNA from various bacteria in a human stool sample and then transferred individual genes into a laboratory strain of *E. coli*. The scientists searched for modified *E. coli* that produced enzymes which stripped the troublesome sugar molecules from type A blood cells. Two enzymes, both from the gut bacterium *Flavonifractor plautii*, were found to work in tandem to eliminate the blood antigens. If the process proves widely viable, it could more than double the currently available supply of universal donor blood.

REFERENCE: Rahfeld P. et al. An enzymatic pathway in the human gut microbiome that converts A to universal O type blood. Nature Microbiology (2019) 4:1475-85 doi: https://doi.org/10.1038/s41564-019-0469-7.

Universal flu vaccine enters first human trial

Flu vaccines are typically tailored to the most likely subtypes of influenza a person will face in the coming flu season. In contrast, a universal flu vaccine could teach the body to create an immune response against multiple strains of the virus, providing lasting immunity across many years.

Flu vaccines cause the body to generate antibodies against a specific part of an influenza protein called hemagglutinin (HA). Made up of a head and a stem, this viral protein helps the influenza virus enter human cells. Because vaccines traditionally target the head - which varies from strain to strain - they must be updated annually to match the varieties predicted to be most prevalent.

Universal vaccines seek to target regions of the HA protein that are shared among influenza strains. By teaching the body to recognize and target this part of the virus, the vaccine equips the immune system to fight a broader range of influenza, providing longer lasting protection. Some use inactivated (killed) viral particles while others use live, but weakened (attenuated) viruses. BiondVax's M-001 vaccine is the first universal vaccine to reach phase 3 clinical trials. A two-year test began in 2018, with results expected near the end of 2020.

REFERENCE: National Institutes of Health. NIH begins first-in-human trial of a universal influenza vaccine candidate. N.p., 3 April 2019. Web. 23 July 2019. https://www.nih.gov/news-events/news-releases/nih-begins-first-human-trial-universal-influenza-vaccine-candidate.

Chinese scientist makes first claim of gene-edited babies

A Chinese scientist captured the world's attention in November 2018 when he claimed, with extremely limited evidence, that he had edited the embryonic genes of twin baby girls born earlier in the month. As of the summer of 2019, the scientist in question has yet to publish a peer-reviewed study on his alleged actions, and the conversation surrounding those actions depends on interpreting a series of slides he presented at a conference.

The work does not appear to have gone through any of the appropriate ethical approvals, and it jumps several steps ahead of accepted practice in genomics research.

He Jiankui, the scientist behind the claim, says he edited embryos which were created through in vitro fertilization. He says the editing was done using CRISPR Cas9, targeting the *CCR5* gene. By disabling *CCR5*, Jiankui aimed to make the twin girls immune to HIV since *CCR5* has been linked to HIV's ability to enter cells. The father of the girls is said to be HIV positive.

The alleged actions of Jiankui earned him a range of criticisms. For starters, there are already known treatments for children with parents who are HIV positive, meaning such extreme measures were less likely to be justifiable. Also, standard ethics protocols were not followed for the experiment, and the ripple effects of CRISPR edits are not totally understood, meaning that it's still not wholly clear what impact the genetic edits could have outside of *CCR5*.

A June 2019 study offered further indictment of Jiankui's alleged actions, finding that individuals with the mutation that Jiankui says he intentionally caused were about 20% less likely to reach age 76 compared to people who did not have two copies of that mutation. The study emphasized the recklessness of embryonic gene editing at this point, especially on such limited information.

Many questions remain about He Jiankui's work, especially since it has not been published. Even with limited details, the scientific community has raised many important questions about the appropriate use of gene editing on human embryos and the clinical and ethical requirements that should be met before additional efforts should even be considered.

REFERENCE: Cryanowski D. The CRISPR-baby scandal: what's next for human gene-editing. Nature (2019) 566:440-442.

More details can be found in the Shareable Science blogpost: What you need to know about the first claim of a genetically-edited baby

HIV successfully edited out of live mice in trial

Scientists have eliminated HIV from some live mice using CRISPR-based gene editing, marking a potential major step forward for treating the disease.

HIV works by hijacking the replication process of the body's cells. Acute HIV infections feature rapid replication of the virus. When HIV transitions into AIDS, that rapid replication is also accompanied by severe damage to the immune system and significant susceptibility to opportunistic infections. In these cases, antiretroviral therapies can be used to control replication and manage symptoms. However, there is no current treatment for latent HIV, where the virus integrates into the cellular genome across a number of organs. Latent HIV does not replicate as quickly, but it also does not leave the body.

Scientists have turned to gene editing to remove the latent HIV from the genome. Using CRISPR Cas9 as a kind of genetic scissors, the researchers were able to snip the HIV from the genome of live mice.

The treatment worked on only a fraction of the mice in the study, so understanding what limited the success of the technique is also crucial to using it more broadly. This is only among the first stages along a long road before the treatment can be used on people, but it is a promising step forward.

REFERENCE: Yin C. et al. In Vivo Excision of HIV-1 Provirus by saCas9 and Multiplex Single-Guide RNAs in Animal Models. Molecular Therapy (2019) 5:1168-86 doi: 10.1016/j.ymthe.2017.03.012.

Gene and cell therapies offer pricey miracles

A recent report identified nearly 300 new gene and cell therapies currently in development. For those who receive the treatments, they can often seem miraculous, especially for diseases where clinicians have had few or no prior options.

Gene therapy was successfully used in one clinical trial to cure X-linked severe combined immunodeficiency (SCID-X1), sometimes called "bubble boy disease." The genetically inherited condition inhibits normal immune function. By taking out bone marrow, introducing synthetic, functional DNA to blood stem cells in that bone marrow, then reintroducing the marrow into the body, scientists were able to restore immune function. The Food and Drug Administration recently approved another gene therapy a little further along the trial process — Zolgensma® treats infants with spinal muscular atrophy, which affects motor neuron function. The treatment works by introducing healthy copies of the affected gene through a virus, and it has led to significant improvement in patients.

Huntington Disease also saw an important trial for a type of gene silencing treatment called antisense oligonucleotide. The treatment works by introducing specifically designed DNA molecules that bind mRNA made by the disease-causing gene, leading to the mRNA's destruction. The trial showed the treatment wasn't harmful to patients and reduced levels of the mutant huntingtin protein were observed in patient's cerebrospinal fluid.

Other promising cell therapies use induced pluripotent stem cells (iPSCs) to replace non-functioning or poorly functioning cells. Pluripotent cells can develop into other kinds of cells, and iPSCs can be generated from other adult cells, making them relatively easy to obtain. Researchers used iPSCs to halt age-related macular degeneration in Japan, successfully reprogramming skin cells to become eye cells. In this first clinical trial, the treatment prevented further vision loss. Scientists have also used iPSCs reprogrammed from donor skin to generate brain cells that were implanted into a patient with Parkinson disease. That trial is in a very early stage and researchers plan to treat an additional six patients by the end of 2020.

These treatments can generate incredible results, but they are also expensive to develop and administer. For example, the single shot required for the spinal muscular atrophy treatment costs $2.1 million, leading some to call it the most expensive shot in the world. The conversations about widespread use of these treatments will have to factor cost in with accomplishment.

REFERENCES: Mamcarz E. et al. Lentiviral Gene Therapy Combined with Low-Dose Busulfan in Infants with SCID-X1. New England Journal of Medicine (2019) 380:1525-34 doi: 10.1056/NEJMoa1815408.

U.S. Food and Drug Administration. FDA approves innovative gene therapy to treat pediatric patients with spinal muscular atrophy, a rare disease and leading genetic cause of infant mortality. N.p., 24 May 2019. Web. 18 July 2019. https://www.fda.gov/news-events/press-announcements/fda-approves-innovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-rare-disease.

Tabrizi S.J. et al. Targeting Huntingtin Expression in Patients with Huntington's Disease. New England Journal of Medicine (2019) 380:2307-16 doi: 10.1056/NEJMoa1900907.

Cyranoski D. 'Reprogrammed' stem cells implanted into patient with Parkinson's disease. Nature (2018) doi: 10.1038/d41586-018-07407-9.

Lack of diversity leaves gaps in genetics research

Genetics research has been largely based on populations of European ancestry. This significantly limits its potential usefulness for everyone.

Across the 3 billion base pairs that make up the human genome, people share 99.9% of their nucleotides. The small regions of difference allow researchers to conduct genome wide association studies (GWAS), hoping to link DNA change to health risks. When studying complex health issues like heart disease, hundreds of genetic markers analyze the constellation of genes that determine a person's risk. However, when looking across ancestries, the necessary data points might occur in different places, altering the shape of the constellation. The most recent GWAS aggregations show that nearly 78% of participants come from white European ancestry. Their findings do not necessarily equally apply to populations outside the original study group.

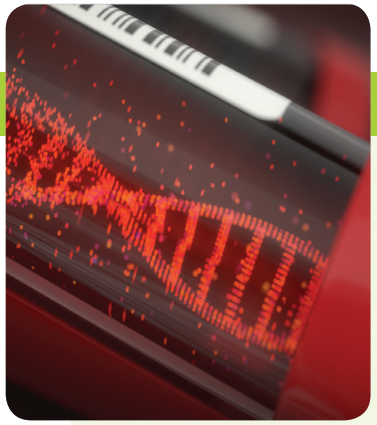
Even fundamental tools, like a reference genome, don't translate universally across ancestry. Research published in November 2018 found that people of African descent had nearly 300 million base pairs of information not represented in the standard human reference genome.

Without diverse sources of genomic information, tomorrow's data-driven, personalized treatments will continue to focus on people of European ancestry, potentially excluding underrepresented populations from these benefits. This imbalance of information hurts other forms of medical discovery as well because diversity often reveals new mechanisms of genetic resilience.

Multiple factors lie behind this information inequality. To date, the expense of genetic testing has restricted its access to the wealthy or well-insured — a population that is disproportionately white. Individuals may be less likely to volunteer for research studies due to fears that their data will be shared with law enforcement or other government agencies. Historical examples of unethical research practices that focused on minority populations is another barrier to participation.

The shortcomings of our current trove of genetic data cannot be overlooked, nor can we underestimate the value of expanding that dataset to include greater diversity. Efforts to overcome these challenges begin by directly involving underrepresented communities in the design and implementation of genomic analyses.

REFERENCE: Sirugo G., Williams S.M., and Tishkoff S. The Missing Diversity in Human Genetic Studies. Cell (2019) 177:26-31 doi: 10.1016/j.cell.2019.02.048.



Polygenic risk scores reveal disease risk, pose risks of their own

Most diseases and health outcomes cannot be narrowed down to changes in a single gene. Instead, they are the result of dozens or even hundreds of genes working together in concert with environmental factors. On their own, each genetic variant has only a tiny influence on disease risk, but the collective impact may be quite large. Polygenic risk scores (PRS) use machine learning and large databases to aggregate the effect of multiple genes for a specific disease. Over the past year, PRS have been created for a variety of health outcomes, from obesity to heart disease, diabetes to depression. They are hypothesized to provide physicians and patients a more accurate estimate of disease risk. Some organizations are even looking to develop web-based platforms that will allow consumers to upload their existing direct-to-consumer genetic information to obtain personal risk scores.

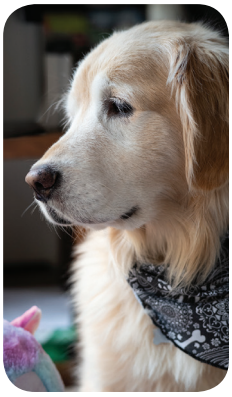
Polygenic risk scores show a lot of promise, because they can help people responsibly monitor the aspects of their health where they are most genetically vulnerable. Sometimes small lifestyle changes can prevent large health complications down the road, leading to better outcomes and lower costs. However, it is also possible those test results cause someone to live in fear of something that never comes to pass, potentially taking drastic steps to stop what might not have been a real threat for them. Conversely, others might ignore signs of a problem because they feel they are not at risk, given their test results showed a low likelihood for a particular outcome. Many researchers feel a larger population of individuals should be tested and followed before PRS are ready for disease prediction and prevention.

These polygenic risk scores show immense potential for creating a more genomically literate society, specifically in regard to the way a person's genome impacts their health. It's important that the score comes with the appropriate guidance though, or else it could wind up doing more harm than good.

REFERENCE: Sugrue L.P. and Desikan R.S. What Are Polygenic Scores and Why Are They Important? Journal of the American Medical Association (2019) 321:1820-21 doi: 10.1001/jama.2019.3893.

More details can be found in the Shareable Science blogpost: AI can now tell your genetic risk for health outcomes like heart disease and depression

Gene editing as therapy for Muscular Dystrophy



A possible treatment for Duchenne Muscular Dystrophy (DMD), the rare and fatal genetic disease in which muscles become weak and nonfunctional, is one step closer. Mutations in dystrophin, a large gene on the X chromosome, are responsible for the symptoms of DMD. Many of these DNA mutations disrupt the reading frame, yielding nonfunctional protein. To explore treatment options, researchers have turned to a population of dogs that develop DMD-like symptoms because of similar inherited DNA changes. Gene editing has been tested on these dogs in an attempt to restore dystrophin function.

The underlying DNA change in the DMD puppies causes a splicing error that not only excludes an entire exon, but also causes a frame-shift in the dystrophin mRNA. CRISPR was used to exclude a second, neighboring exon, restoring the reading frame. Although missing two internal exons, the edited protein is still capable of performing its shock-absorbing function in muscles.

Affected puppies were injected with viral vectors containing the editing system. No evidence of off-target DNA changes was observed. Treated muscles began producing functional dystrophin within a few weeks and the treated puppies showed increased play activity. In one dog, dystrophin expression was 3-90% of the level seen in unaffected dogs for various skeletal muscles, 58% for diaphragm and 92% for heart. Although the sample size is tiny, and longer-term study is needed, these are exciting preliminary results.

REFERENCE: Amoasii L. et al. Gene editing restores dystrophin expression in a canine model of Duchenne muscular dystrophy. Science (2018) 362:86-91 doi: 10.1126/science.aau1549.

Set of projects show value, limits for genetic sequencing of newborns

The National Institutes of Health funded a series of four projects in 2013 with the shared goal of studying the use of genetic sequencing for newborns. The program, called NSIGHT, summarized findings in June 2019. While sequencing shows great promise as a tool for quick diagnosis of acutely ill newborns, the practice likely isn't ready to replace the standard newborn screening tests.

For one dataset, initial sequencing was used on 35 infants admitted to the neonatal intensive care unit (NICU). Of those 35 babies that received whole-genome sequencing, 20 also received a diagnosis, 11 got a change in care management, four had improved outcomes and one life was saved, according to the clinicians running the program.

Sequencing was expanded to a larger group in order to survey parents and clinicians on how useful they found the test. Both parents and medical professionals agreed the sequencing was useful, with those caring for the sickest children the most likely to find the tests to be valuable. Parents even felt that negative reports were helpful. Analysis of results continues, specifically in regard to cost effectiveness.

Researchers did note that sequencing is most helpful in unique cases. For the vast majority of infants, current newborn screening protocols are highly effective and cost efficient. Newborn sequencing has a lot to offer, but it isn't ready to be elevated to the first line of defense.

REFERENCE: The NSIGHT program held a public webinar June 24, 2019 to discuss findings from the four funded projects. Videos of each session can be found at https://www.genome.gov/event-calendar/NSIGHT-Final-Public-Session.

Fruit flies used to create personalized treatment for patient with drug-resistant cancer

Colorectal cancer is one of the most lethal cancers in the world and the second leading cause of cancer mortality in the United States. This type of cancer remains so deadly in large part because it adapts quickly, thwarting treatment. A paper published in May 2019 described a patient with advanced colorectal cancer who had received multiple rounds of chemotherapy, but his tumors did not respond. In an attempt to find an effective therapy, researchers used fruit flies engineered to carry his specific cancer mutations to identify a custom drug cocktail, which shrank his tumors for several months.

The scientists performed whole-exome sequencing on DNA from the 53-year-old man's primary tumor. They found more than 100 cancer-associated mutations. The researchers then focused on likely drivers—narrowing the list to six genes. They then added three likely contributor genes in which the patient had inherited mutations.

Creating a successful model for resistant cancers can be difficult, and each approach comes with different challenges. Growing cells in cultures fails to capture the complexity of the body; creating mouse models takes months and is expensive. In this case, researchers took the nine genetic mutations and modified the hindguts of fruit flies to recreate the patient's DNA profile. The scientists then tested 121 different FDA approved drugs on the flies, searching for medications that increased fly survival. They ultimately settled on a combination of two of them.

When the scientists used those two drugs on the patient, his tumors shrank by 45 percent. For three months no growth was observed, following eight months of slow growth. Ultimately, new tumors appeared and the patient was switched to another treatment protocol.

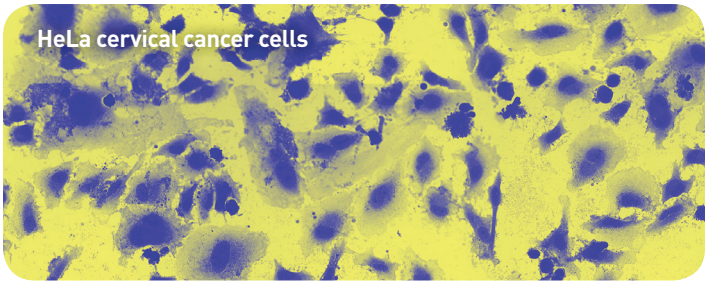
With only a single patient, and no controls, significant questions remain before this approach can be routinely considered. Still, this work serves as a powerful proof of concept for mimicking the complex nature of cancer in order to better screen for effective treatments.

REFERENCE: Bangi E. et al. A personalized platform identifies trametinib plus zoledronate for a patient with KRAS-mutant metastatic colorectal cancer. Science Advances (2019) 5:eaav6528 doi: 10.1126/sciadv.aav6528.

Cells from oldest immortal human cell line differ from lab to lab

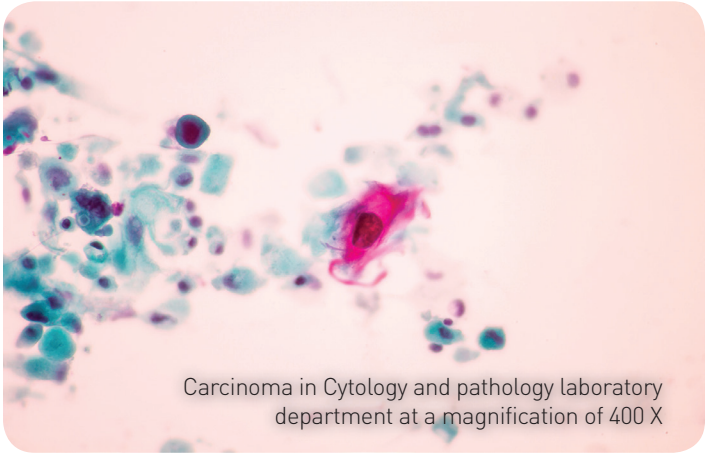
A February 2019 study shows that HeLa cells, which have been used in a wide variety of experiments for more than 70 years, vary dramatically between labs. The finding may challenge the reproducibility of research done using the line.

The HeLa cell line started with cells collected from a cancerous cervical tumor from Henrietta Lacks, without her knowledge, in 1951. Those cells were found to be immortal, meaning that unlike typical cells, they did not die after a set number of cell divisions. Thought to represent a seemingly inexhaustible supply of unchanging cells, HeLa cells have been used for a broad array of research, including the development of a polio vaccine.



HeLa cervical cancer cells

Now researchers say the cell line has evolved significant differences across the samples. The researchers compared the genomes of 14 HeLa samples from 13 labs in six countries. Despite handling the various samples under the same conditions, they found genetic differences that resulted in obvious physical differences. For example, some of the cell populations doubled in a little more than 17 hours, while others took 32 hours. Different populations responded differently to Salmonella exposure. As cells were cultured, their gene expression profiles changed over time. The results were so stark that one author speculated that conducting identical experiments six months apart with the same cell line might actually yield different results.

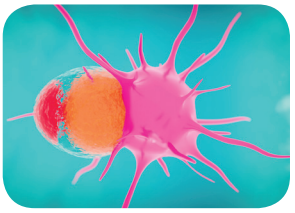


Carcinoma in Cytology and pathology laboratory department at a magnification of 400 X

The research raises questions about the HeLa cell line, but it also brings larger questions about reproducibility into focus. It's not enough to know that the HeLa line is mutating. It's possible there are factors in these labs contributing to that mutation. Learning to identify what those factors might be could help improve reproducibility in the scientific community.

REFERENCE: Liu Y. et al. Multi-omic measurements of heterogeneity in HeLa cells across laboratories. Nature Biotechnology (2019) 37:314-22 doi: 10.1038/s41587-019-0037-y.

Thousands of *BRCA1* variants classified



BRCA1 is a widely known gene associated with breast and ovarian cancer. This gene functions normally as a tumor suppressor. Genetic mutations can cause *BRCA1* to lose function, contributing to the formation of these deadly cancers. Now scientists have a tool to help classify which mutations result in that dangerous loss of function.

Thousands of variants in *BRCA1* have been identified across the human population, but the cancer-causing probability of many of them are unknown. To help solve this ambiguity, researchers engineered and analyzed the functional impact of nearly 4,000 single nucleotide variants within key parts of the *BRCA1* gene. Each change was integrated into a human cell line that was programmed to die in the presence of a nonfunctional *BRCA1*. The researchers found approximately 700 of the variants affected function.

When a testing lab identifies a variant in a gene of known importance like *BRCA1*, but the evidence of that variant's disease-causing impact is lacking or conflicting, it is classified as a variant of uncertain significance (VUS). Observing the variant in more than one patient strengthens the likelihood it actually is disease-causing. But many variants are rare and the lack of repeated observation can leave patients with a VUS struggling for answers. This study offers an important piece of functional evidence to help classify those DNA changes.

REFERENCE: Findlay G.M. et al. Accurate classification of BRCA1 variants with saturation genome editing. Nature (2018) 562:217-22 doi: 10.1038/s41586-018-0461-z.

Mutations in normal cells could help with early cancer detection

Early cancer detection remains a critical goal for medicine, as earlier recognition of cancer generates better results for patients. Advancements in sequencing technology and major cancer research projects have allowed us to study fully-developed tumors more completely, giving a better developed picture of the mutations in those tumors. However, in order to use that information for early detection, we must also know which mutations occur in normal cells.

A study published in July 2019 examined somatic mutations, those that occur in body cells and often in response to environmental factors. Researchers discovered these mutations lurking in otherwise normal tissue across 95% of the 500 person cohort. Sun-exposed skin, the lining of the esophagus, and the lungs all showed higher rates of somatic mutation, which points to contributing environmental factors like ultraviolet light, air pollution, smoking and eating habits. A correlation was also found between the individual's age and the overall number of mutations.

Many of those mutations will not lead to cancer, though it's likely some will. The study calls for even more extensive sequencing of normal tissues and pre-cancerous lesions in order to compare the various factors surrounding somatic mutations - exposure to environmental mutagens, natural cellular architecture and rate of cell division.

Differentiating between somatic mutations that lead to cancerous cells and those that do not may lead to tests that predict the development of cancer much earlier.

REFERENCE: Yizhak, K. et al. RNA sequence analysis revealsmacroscopic somatic clonal expansion across normal tissues. Science (2019) 364:eaaw0726 doi: 10.1126/science.aaw0726.

Body uses sleep to repair damaged DNA

Scientists have demonstrated that damaged DNA gets repaired during sleep, helping craft at least a partial theory of sleep's importance across the animal kingdom. The researchers behind the study genetically engineered small, transparent zebrafish to have colorful chemical tags on the chromosomes in their neurons. The tags allowed scientists to track the chromosomes using a specialized microscope.

When the fish were awake, scientists observed that the tagged chromosomes moved very little. DNA strands, which break as part of the normal wear-and-tear of life, became damaged and built up in the neurons of the fish. If the researchers kept the fish awake by tapping on the tank, the damaged DNA would build up to the point that some neurons were at risk of dying off altogether.

After the fish went to sleep, their neuronal chromosomes moved more rapidly, bending and wriggling. During sleep, the level of chromosome movement essentially doubled. Simultaneously, the amount of DNA damage dropped. Introducing a drug into the tank to make the fish sleep during the day led to similar results. By shifting the chromosome's position, the machinery of DNA repair could better access the damage present at different points along the DNA strand.

The experiment showed the fish engage in a constant struggle to repair DNA as quickly as it is damaged. While awake, the repair systems couldn't keep up, but during the calm of sleep, the fish could catch up to the workload.

The researchers suggest that when neurons accumulate a certain level of DNA damage, they somehow signal the brain that sleep is required to allow for repair. These findings reveals some of the necessity of sleep, and help inform further research into the effects of short and long term sleep deprivation.

REFERENCE: Zada D. et al. Sleep increases chromosome dynamics to enable reduction of accumulating DNA damage in single neurons. Nature Communications (2019) 105:895 doi: 10.1038/s41467-019-08806-w.

First gene-edited food

The first genome-edited food product hit the commercial market in early 2019. Calyxt®, an agriculturally focused biotech company, produced gene-edited soybean oil, which it sold to restaurants for frying, salad dressings and sauces under the name Calyno Oil. The company compares it to sunflower and olive oil but with three-times the fry life and longer shelf life. Calyno Oil contains roughly 80 percent greater levels of oleic acid, reduced amounts of unsaturated fat and contains no trans fats per serving. The company says they are responding to consumer pressure for "healthier food options", as well as the 2015 FDA mandate to reduce the use of trans fats. In March 2019, the FDA authorized the use of qualified health claims and 'heart healthy' labels for Calyno Oil.

The soybeans were edited using transcription activator-like effector nucleases (TALEN) — enzymes that make targeted double-stranded breaks in DNA. The cell's DNA repair mechanisms respond to fix the break, but a few nucleotides are lost in the process, inactivating gene function. Pre-dating CRISPR, TALEN genome editing can be used to silence genes or make small directed changes to the nucleotide sequence. The TALEN-edited soybeans silence two genes that play a role in fatty acid synthesis.

Products of genome editing must meet the same standards as any food item, but under current USDA guidelines the soybeans are not regulated like other products of bioengineering and do not carry the "GMO" label. There is an estimated $150 million price tag for the development of a more traditional transgenic crop, with more than a quarter of that expense required for regulatory testing and approval. In contrast, the cost to develop a genome-edited crop could be as much as 90% lower and could make it to market five years faster. Companies like Calyxt claim that using genome editing technology allows the production of new foods quicker and more cost-effectively, without introducing foreign DNA or changing the taste of familiar products. Less than a year after the introduction, Calyno oil is being purchased by more than two dozen companies, including Sysco, the world's largest foodservice distributor.

REFERENCE: Calyxt. First Commercial Sale of Calyxt High Oleic Soybean Oil on the U.S. Market. N.p., 26 Feb 2019. Web. 24 July 2019. https://calyxt.com/first-commercial-sale-of-calyxt-high-oleic-soybean-oil-on-the-u-s-market/.

Bioengineered food labels

The United States Department of Agriculture recently announced requirements for labeling bioengineered foods that will go into effect at the start of 2020. The term 'bioengineered' refers to food commonly called GMO's — genetically modified organisms. More specifically, bioengineered foods have undergone transgenesis — a specific type of genetic modification where DNA sequences from another organism are added to the genome to change some important characteristic or trait. These modifications could increase yield, improve pest resistance, create herbicide tolerance or even prevent browning.

In 2016, Congress tasked the USDA with developing labeling standards for bioengineered food. The USDA determined that only foods that either resulted from transgenesis or included an ingredient resulting from transgenesis would require special labeling, found next to the nutritional information panel or on the front of the package.

The USDA keeps a list of foods that come in bioengineered varieties. As of Summer 2019, that list includes certain types of alfalfa, apples, canola, corn, cotton, eggplant, papaya, pineapple, potato, salmon, soybean, squash and sugarbeets. The current USDA list, along with additional details about each crop, is at https://www.ams.usda.gov/rules-regulations/be/bioengineered-foods-list.

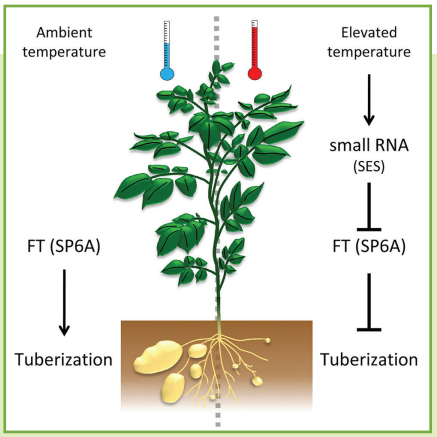
There are a handful of exceptions to the labeling requirements. For example, non-food products made from bioengineered foods won't be labeled. Neither will products from animals given bioengineered feed, as the bioengineered DNA is broken down by the animal's digestive system. Because their genetic material is removed during preparation, highly-processed foods like corn syrup or soybean oil aren't required to carry the label, even if derived from bioengineered plants. The labeling rules also won't apply to foods developed through the newer "gene-editing" techniques like CRISPR, because they don't contain DNA from other organisms and mimic the spontaneous genetic variation that occurs through natural selective breeding. Some manufacturers have announced their intention to voluntarily disclose the presence of these exceptions alongside those required by law.

That labeling comes in 4 potential forms:

- **Symbols:** There are accepted symbols that say either "Bioengineered" or "Derived from Bioengineering."
- **Text Label:** Producers can put text on product packaging that says "Bioengineered" or "Contains a Bioengineered Food Ingredient."
- **Digital:** Producers can make their package scannable, either through QR codes or by developing new technology. In this case, they can simply say "Scan for more food information" on the label. If they use a scannable label, they are also required to include a phone number, which must be able to provide that same information to consumers 24/7.
- **Text Message:** Producers have the option to list a phone number for shoppers to text for more food information. That number would immediately respond in a text message with the same information you would get by scanning the product with a digital label.

More details can be found in the Shareable Science blogpost: A guide to how GMO's and bioengineered foods get labeled

Warm weather spuds



Potatoes stand with corn, rice, wheat and cassava as vital staple foods. More than 300 million metric tons of potatoes are produced annually. Potatoes thrive in colder temperatures. Agriculturally important potato varieties grown in warmer temperatures behave differently, producing more leaves and shoots but forming few if any tubers. The tubers that do form are often smaller, contain less starch and sprout quickly, making those potatoes less nutritious and prone to rot much faster. Before 2018, the mechanism for this growth difference was unknown, but becoming increasingly important for growers to uncover.

German scientists discovered a small RNA, containing only 19 nucleotides, that plays a critical role in this temperature-dependent change in tuber production. At the right temperatures and right length of day, potatoes produce a protein called SP6A, that induces tuber formation along the roots in preparation for colder winter periods. At warm temperatures, the small RNA effectively blocks SP6A production, preventing the tuber formation signal.

Building on this discovery, the researchers developed potato plants in which this small RNA was deactivated. In the greenhouse, these plants produced high-quality tubers under much warmer temperatures. While yet to be tested in the field, blocking the small RNA could ensure the stability of the potato crop under increasing global temperatures.

REFERENCE: Lehretz G.G. et al. Post-transcriptional Regulation of FLOWERING LOCUS T Modulates Heat-Dependent Source-Sink Development in Potato. Current Biology (2019) 29:1614-24 doi: 10.1016/j.cub.2019.04.027.

Hi-Res peanut genome decoded

Peanuts are the product of hybridization between two different species. Initial sequencing work had uncovered one of the ancestral species, but the other remained a mystery. Using new sequencing technologies and computational tools, researchers have assembled a much higher resolution peanut genome. This genome reveals parts of the plant's DNA that control traits like seed size and disease resistance but also sheds light on the dawn of peanut agriculture in South America.

The newly discovered second ancestor didn't grow in the same region as the first ancestral plant. Evidence suggests that humans carried and cultivated the A genome plants into the B genomes' home range, providing the opportunity for the two to cross-pollinate. Interestingly, all modern peanut strains bear the genetic signature of this single hybridization event. Most flowering plants rely on animals or weather to spread seeds, generating genetic diversity and spreading newly occurring traits. Peanuts, however, produce seeds underground and rely on humans for long-distance transport. How can a single small population of peanut plants, even hybrids, evolve into the hundreds of peanut varieties grown across the world today?

This answer also can be found in the peanut genome. Analyzing more than 200 types of peanuts from all over the word showed that different varieties had shuffled the genetic material from the ancestral strains. This shuffling has occurred thousands of times producing much faster genetic diversity than could be predicted by mutation alone.

REFERENCE: Bertioli D.J.. et al. The genome sequence of segmental allotetraploid peanut Arachis hypogaea. Nature Genetics (2019) 51:877-84 doi: 10.1038/s41588-019-0405-z.

The laboratories of HudsonAlpha faculty researchers Jane Grimwood PhD and Jeremy Schmutz contributed to this research.

Creating edible cotton

Cotton is grown on six continents and provides fibers for textiles and other industrial uses. For every pound of fibers produced, the plants make 1.6 pounds of seed. Cotton seeds contain relatively high amounts of protein (23%) making them a potential food source for livestock and humans. While cottonseed contains many valuable nutrients, it also holds toxins. One of those toxins, gossypol, is a yellowish pigment that serves as a natural insect deterrent. Unfortunately gossypol is toxic to humans, causing red blood cells to rupture. Cottonseed oil has been used in human products such as mayonnaise and cosmetics for 20 years, but the oil must first be distilled to remove gossypol. Much of the mass of cottonseed is discarded as waste.

Researchers from Texas A&M have developed a transgenic cotton variety that produces dramatically reduced amounts of gossypol in the seed. RNA interference (RNAi) disrupts a critical enzyme involved in gossypol production within seeds. This cotton has typical gossypol content in other parts of the plant, maintaining the pest resistance. Reduced gossypol in the seed makes the oil distillation process more straightforward and less expensive. The seed has so little gossypol that it meets the WHO standards for human food. In 2018, the USDA ruled this bioengineered variety would no longer require an additional level of oversight. Ultra-Low-Gossypol-Cottonseed can be used as feed for livestock or ground into protein-rich flour for human consumption. Researchers hope this product enables the production of fibers, oil, livestock feed and food in a single crop without the need for additional water, fertilizer or insecticide.

REFERENCE: U.S. Department of Agriculture. USDA Announces Deregulation of GE Low-Gossypol Cotton. N.p., 18 October 2018. Web. 25 July 2019. https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/brs-news-and-information/2018_brs_news/texas_am_low_gossypol_cotton

The Human Microbiome

Imagine a thriving metropolis, inhabited by millions. Like many large communities, it's grouped into distinct neighborhoods – the upper East side, Old Town, the manufacturing district, the high rises along the waterfront. Over time, neighborhoods transition as a new group of tenants replaces the previous residents. Periodically, periods of civil unrest sweep through the region, leading to the displacement of entire populations. Afterwards, a period of calm restores equilibrium.

This is the story of our microbiome: the collection of microscopic organisms found on our skin, throughout our digestive system and inside various body cavities like our mouth and nose. We serve as the infrastructure for these thriving communities, providing nutrients and a favorable climate for growth. In turn, the vast majority of these microbial inhabitants are beneficial to our daily existence. So put down the antibacterial hand sanitizer and learn more about your microbial hitchhikers.

By the numbers

39 trillion bacterial cells

300 trillion viral particles

unknown number of fungi & other microbes

Where it's found

Microbial communities are found wherever the body comes into contact with the outside world. It's estimated that up to five pounds of microorganisms live in and on the human body.

nasal passage, mouth, teeth, tongue, cheeks, lungs, skin, digestive system, urogenital tract

How it's shaped

At Birth

The manner of birth significantly impacts what microbes initially take up residence in the gut. Vaginal-born babies have *lactobacillus*, *prevotella* and other *bifidobacterium* strains – bacteria which may not appear in the gut of babies born by Caesarean section for several months.

Early Life

The gut microbiome differs between infants who are breast or bottle fed. More than one-quarter of the gut bacteria from breast-fed infants are naturally found in breastmilk. The composition of the gut microbiome dramatically shifts as solid foods are introduced.

Teen/Adult

Without intervention, most microbial populations are stable throughout adulthood. Dietary changes can alter gut microbial populations. Recent evidence suggests skincare products like cleansers and antiperspirant can similarly alter the skin microbiome.

Elderly

Preliminary data suggests gut microbial diversity declines with age, possibly accelerated by the increasing use of medication. At the same time, the presence of harmful bacteria increases. Intestinal walls can become leaky, leading to inflammation and autoimmune disorders.

Ways it benefits us

harvests additional energy from food

aids movement of food and waste through the gut

produces vitamins and hormones

influences behavior

defends against harmful infections

trains the immune system to distinguish friend from foe

When it's disturbed

Disturbances in our microbial communities have been associated with the following disorders. For many, it's still not clear if the altered microbiomes are the cause or a consequence of the condition.

accute respiratory infection
allergies
Alzheimer disease
amyotrophic lateral sclerosis
anxiety
autism
autoimmune disease
cardiovascular disease
cirrhosis
C. difficile infections
colon cancer
diabetes
depression
hepatocellular carcinoma
inflammatory bowel disease
irritable bowel syndrome
obesity
Parkinson disease
premature birth
schizophrenia

Want more information about the microbiome? Check out HudsonAlpha's 2019 Biotech 201 series on YouTube.

How it can be altered

Antibiotics
destroy or inhibit the growth of bacteria – the beneficial strains as well as the harmful ones

Probiotics
live microorganisms that are intended to have health benefits when consumed or used on the body

Prebiotics
nondigestible food components that selectively stimulate the growth of beneficial microorganisms

Diet
Western diets lower the diversity of gut bacteria and increase immune gut inflammation. Mediterranean and plant-based diets increase diversity and lower inflammation.

Exercise
regular exercise increases gut microbiome diversity and strengthens the gut barrier

Stress
psychological stress alters gut microbial populations, affecting the levels of neurotransmitters produced by gut bacteria

Microbial transplant
microbes obtained from the stool of a healthy person are transferred to a patient to treat disease

HudsonAlpha has provided this material for educational purposes. It is not intended to substitute for the medical advice of a health care provider. Talk with your doctor before any attempt is made to modify your microbiome.

Digital Applications

iCell

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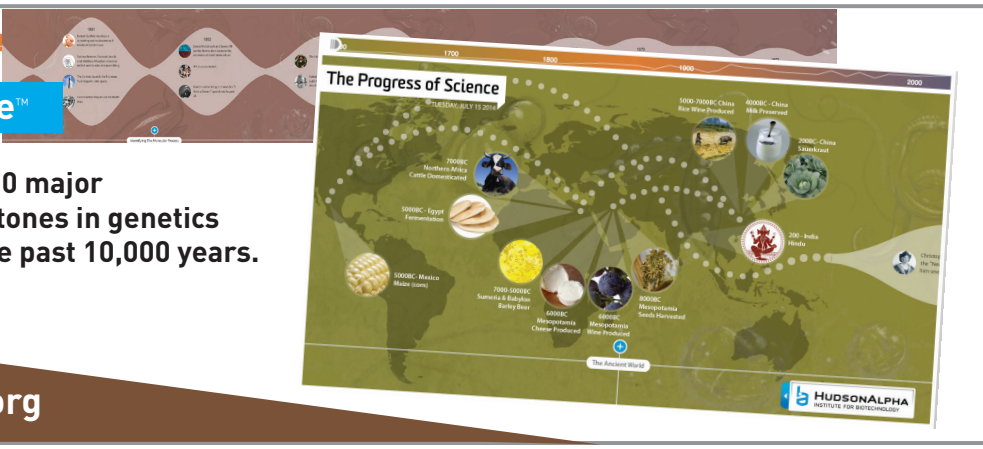

This timeline details over 200 major accomplishments and milestones in genetics and biotechnology during the past 10,000 years.

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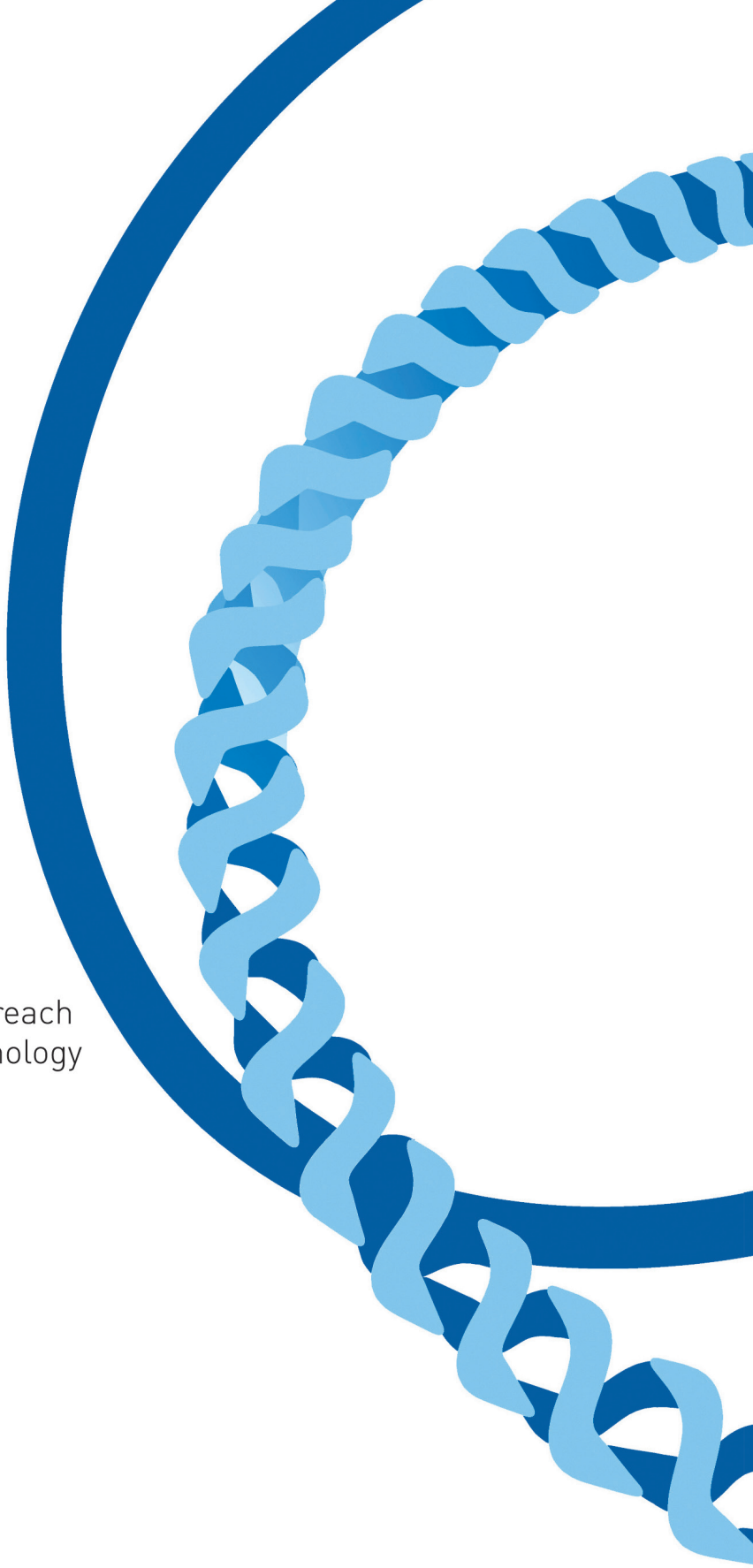

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