BIMM 194: **GENOMICS, BIG DATA AND HUMAN HEALTH** (Winter 2018)

Lecture 1 Homework

https://bioboot.github.io/bimm194_W18/

Dr. Barry Grant (bjgrant@ucsd.edu)

Overview:
Almost daily we hear about the impact of genomics on healthcare and how gene-directed diagnosis and therapies are transforming our understanding of widely divergent fields of medicine.

In this document I share with you some of the stories from the last year that I found particularly interesting. These stores exemplify the extent to which genomics is going to change the lives of patients and healthcare professionals.

Homework:
Before next week's class write and email me (bjgrant@ucsd.edu) a paragraph of 250 words or less detailing which of these stories interests you the most and why? Have any other stories about genomics in the press caught your eye recently? Feel free to write about these for bonus points.

1. Editing the Embryo:

Just imagine if you could correct a genetic disease right there in the embryo, before the condition even developed. It may sound like science fiction, but this tantalizing idea edged closer to potential reality over the past few months following ground-breaking work on human embryo genome editing.

In August, a collaboration from the USA and Korea reported the successful modification of human embryos to remove a genetic mutation causing an inherited heart condition, hypertrophic cardiomyopathy (HCM).

The team used the **CRISPR-Cas9** gene-editing tool to fix a genetic mutation carried by the sperm, using healthy DNA from the mother's egg as the template.

The work was reported in the journal Nature and covered by The Guardian newspaper. For the full story on this breakthrough and discussion of the ethical issues surrounding it, enjoy Hannah Devlin's excellent podcast.

In fact, embryo editing has hardly been out of the news recently. For example, A team in China has successfully used a modified gene-editing tool to correct a point mutation causing β-thalassaemia in human embryos.

Meanwhile, researchers based at the Francis Crick Institute in London are using gene editing in human embryos to investigate genes that are critical in the first hours of life, in order to better understand miscarriage and improve the success rates of fertility treatment.

Legislation around human embryo research currently prevents any modified embryos being allowed to develop into babies and we are a long way from even the suggestion that gene editing would be safe to do in this context. However, if in future the safety concerns are addressed, a bioethical debate of huge proportions looms.

Whilst some might be comfortable with the safe eradication of serious and life-limiting genetic conditions from human embryos, many would be justifiably concerned about the potential of this technology to create '**designer babies**'.

Where do you stand?

2. DIY Crispr: biohacking your own genome

With do-it-yourself Crispr kits now available online. Is it apparently possible to edit your own DNA, is it safe and how should it be regulated?

In October, biohacker Josiah Zayner gave a lecture in San Francisco in which he claimed to be the first person known to have edited his own DNA using **CRISPR** technology. He insists it's something anyone can do using one of his company's gene engineering kits. But does this do-it-yourself approach have any evidence to back it up? Is it safe? And, ultimately, does this kind of self-experimentation drive science forward or expose the public to unacceptable risks?

3. Direct-to-consumer testing

Direct-to-consumer (DTC) testing came under fire recently with the publication of a paper in the journal, Future Medicine, highlighting the lack of support around the genetic testing process offered by DTC companies, and calling for them to make pre-test and post-test counseling available to their consumers.

The findings were reported in The Guardian, where the potential for serious incidental findings to emerge from DTC testing, was highlighted using the example of individuals embarking on DTC for "*a bit of fun*" to explore their ethnic roots but then stumbling across information about their risks of developing Alzheimer's disease.

Have you been tempted to undergo DTC genetic testing? Were you aware that in doing so you might reveal that you had an 80% risk of developing Alzheimer's disease by the age of 80? Still tempted?

4. Who has the right to know your genetic test results?

If a relative receives a genetic test result that has potential implications for you but chooses not to share it, do the doctors have a duty to disclose the information anyway? As things stand, absolutely not.

This principle came under fire earlier this year when a woman, known only as ABC, won her appeal in the high court for the right to sue three NHS Trusts for damages, for not disclosing her father's genetic condition, which had implications for her and her unborn child.

In 2007, ABC's father killed his wife (ABC's mother) and was convicted of manslaughter on grounds of diminished responsibility. Following the incident, doctors noticed he had signs of Huntington's disease, a devastating genetic condition causing late-onset progressive cognitive and motor decline and behavioral changes, for which there is no cure. Genetic testing in 2009 confirmed the diagnosis.

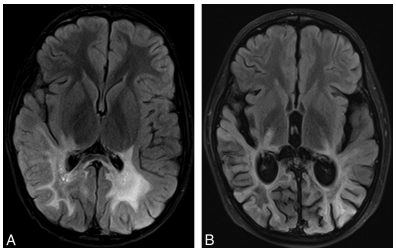
His doctors requested his consent to disclose this result to his daughter, who was now six weeks pregnant and was at 50% risk of inheriting the condition. He refused. ABC's baby was born in 2010, and subsequently one of her father's doctors accidentally disclosed his diagnosis of Huntington's disease to her. ABC was then tested and told she had inherited the Huntington's disease gene expansion.

ABC is now suing the UK hospital trusts involved for damages as she feels that, in light of her pregnancy, she should have been informed of her father's diagnosis. She claims she would have been tested herself as soon as she found out and, as a single mother, if the diagnosis had been confirmed she would have terminated the pregnancy rather than risk her child becoming an orphan or inheriting the condition.

The case was initially rejected, but on appeal to the high court it is now being allowed to go to trial. Would you like to be a juror in this one? Where do you stand?

5. Gene therapy for Cerebral Adrenoleukodystrophy (CALD)

There was another success story for gene therapy recently with the publication by researchers from Boston Children's Hospital of the results of gene therapy trial for CALD, an X-linked neurodegenerative disease affecting young boys.



CALD is a devastating condition caused by mutations in the *ABCD1* gene, leading to the build up of damaging fatty acids in the brain, with progressive demyelination and neurodegeneration. Affected boys typically develop symptoms between the ages of 4 and 10 years, most only surviving a few years from the onset of disease.

Until now the only treatment has been stem cell transplant from a matched donor, which may not always be available and carries all the potential for complications of an allogenic transplant (*i.e.* one coming from another person), such as graft-vs-host disease.

In this trial, reported in the New England Journal of Medicine, clinicians collected the patient's own stem cells, used a lentiviral vector to insert a correct version of the faulty gene, then re-infused the cells back into the patient. Results so far are impressive, with 15 out of 17 boys having stable neurological function 2 years after treatment.

6. Older fathers pass on more mutations

It has long been recognized that certain genetically influenced conditions presenting in childhood such as intellectual disability and autism are more common in children from older fathers. A possible explanation for this phenomenon was described recently in a study suggesting that fathers accumulate and pass on mutations at a faster rate with increasing age than mothers.

In a research study from Iceland, published in Nature, researchers sequenced the genomes of 14,000 Icelanders and their parents, isolating *de novo* mutations and determining the parent of origin.

They found that whilst the number of *de novo* mutations inherited from mothers increased by 0.37 per year of age, the number inherited from fathers increased by 1.51 per year of age.

An article in The Guardian reporting the study commented that these figures mean that 'a child born to 30-year-old parents would, on average, inherit 11 new mutations from the mother, but 45 from the father'. And this discrepancy would only further increase with increasing age.

The authors hypothesize that one explanation for this could be that whilst women are born with their eggs already *in situ*, men continue to make sperm throughout their lives, during which time more mutations can accumulate.