

# At breakneck speed - the remarkable history of genomic medicine over the last 30 years

Cris Print    March 2024



# Plan

- Introduction
- The march of technology
- Applying these technologies for patients
- Genomics examples
- Where to now?

# The march of technology



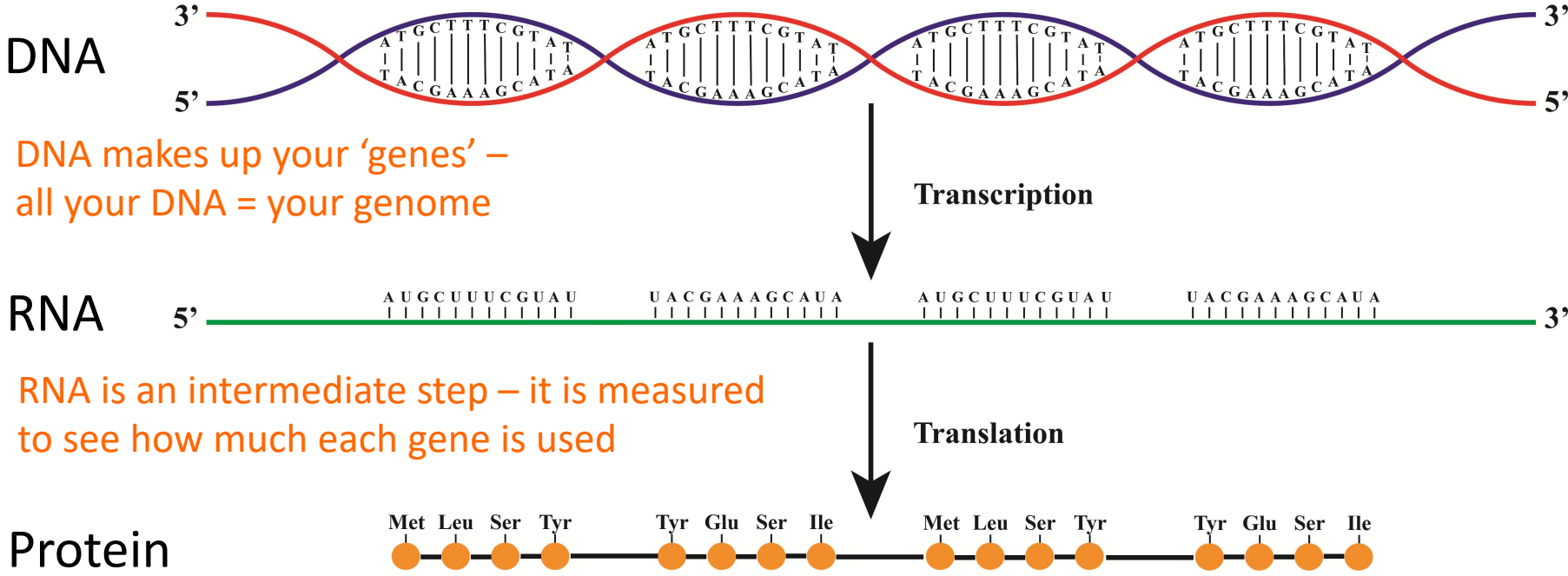


# Introduction

- When I qualified in medicine in 1989 I was fascinated by genes and genomes, however at that time the field of genomics had relatively little to offer most patients
- Fast forward 30-odd years to today, and the advances in what we can do using genomic technologies in medical care and medical research are astounding, with technological developments still accelerating



# Your DNA code (your genes) is used as a template to build proteins in your cells

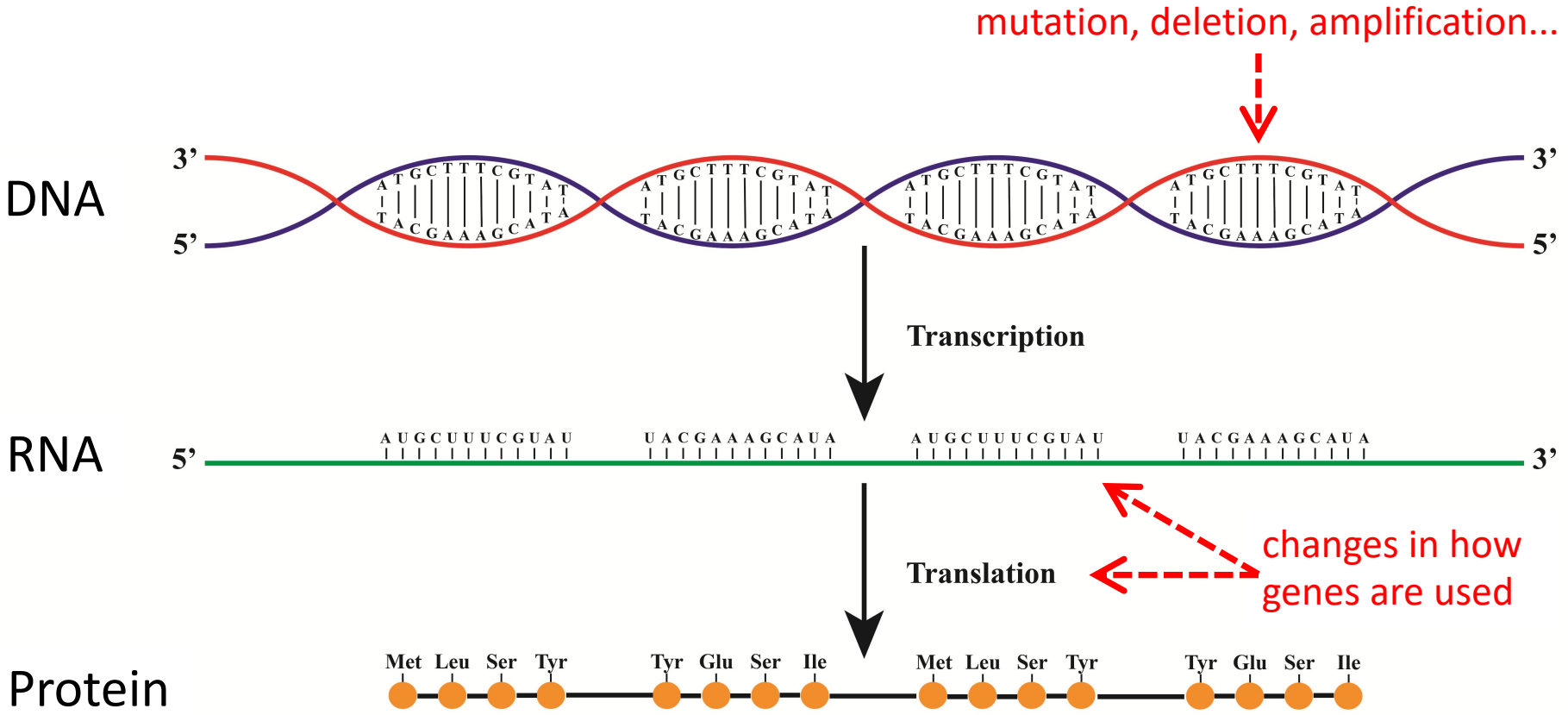


modified from [www.science-explained.com](http://www.science-explained.com)

Minute differences between the DNA  
and RNA of your and my body defines  
our uniqueness

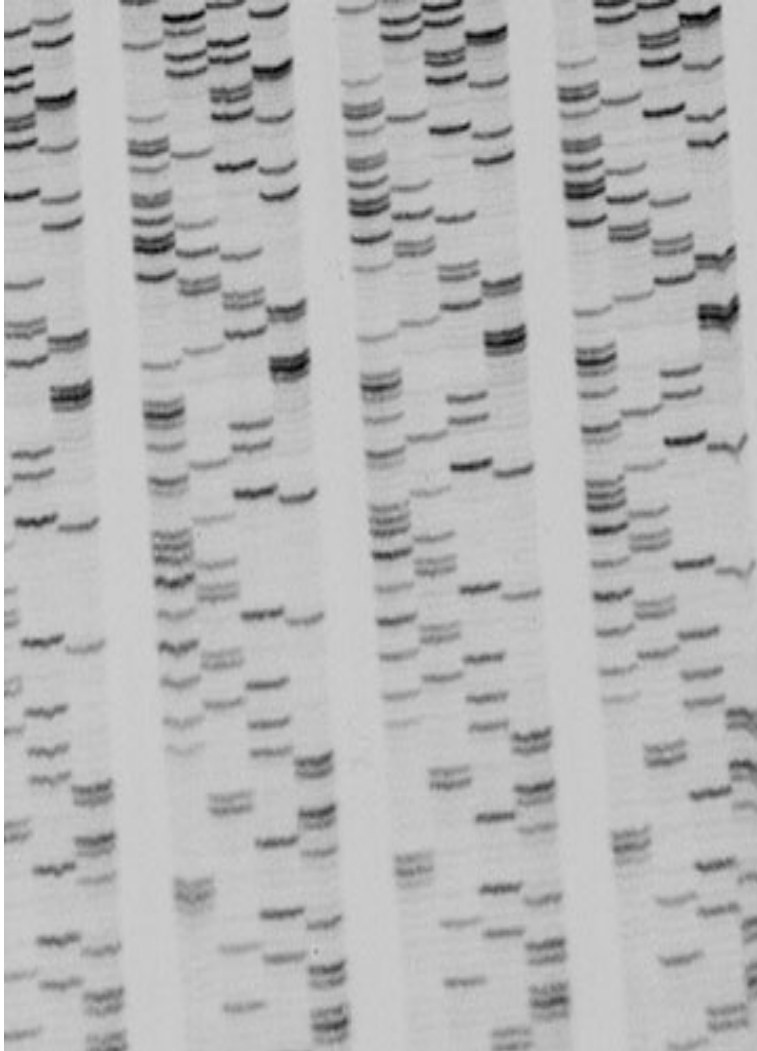
However, these differences can also  
cause disease

# Your DNA code (your genes) is used as a template to build proteins in your cells



modified from [www.science-explained.com](http://www.science-explained.com)

# Progressive advances in genomic technologies: a genomics PhD in 1993



*Gene*, 144 (1994) 221–228  
© 1994 Elsevier Science B.V. All rights reserved. 0378-1119/94/\$07.00

GENE 07997

Cloning of a gene encoding a human leukocyte protein characterised by extensive heptad repeats

(Activation; cDNA; coiled-coil; myosin; peripheral blood cells)

Cristin G. Print, Euphemia Leung, Jane E. B. Harrison, James Douglas Watson  
and Geoffrey W. Krissansen

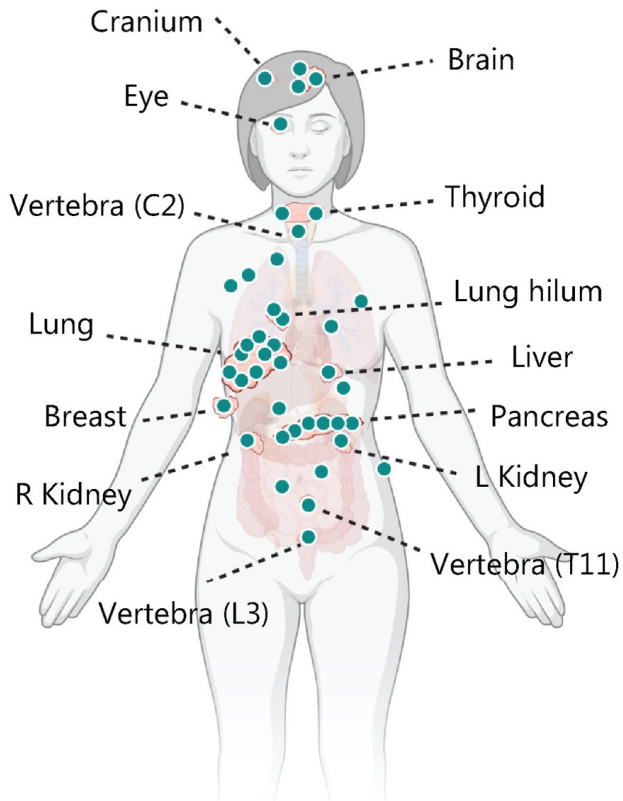
*Department of Molecular Medicine, University of Auckland, Auckland, New Zealand*



Home Analysis Tools Release Note

**KTN1** Gene - Kinectin 1

# Progressive advances in genomic technologies: a genomics PhD in 2023



- DNA Whole Exome Sequencing
- 10x Linked Read Sequencing
- Targeted cfDNA Sequencing
- RNA Expression Arrays
- RNA Sequencing
- Methylation Analysis

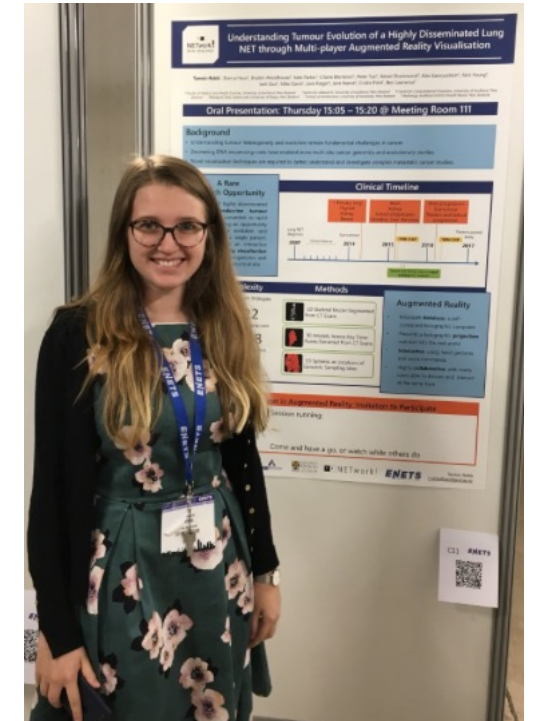
**CANCER RESEARCH COMMUNICATIONS**

**AAGR**  
American Association  
for Cancer Research

RESEARCH ARTICLE <https://doi.org/10.1158/2767-9764.CRC-22-0101> OPEN ACCESS

**Complex Patterns of Genomic Heterogeneity Identified in 42 Tumor Samples and ctDNA of a Pulmonary Atypical Carcinoid Patient**

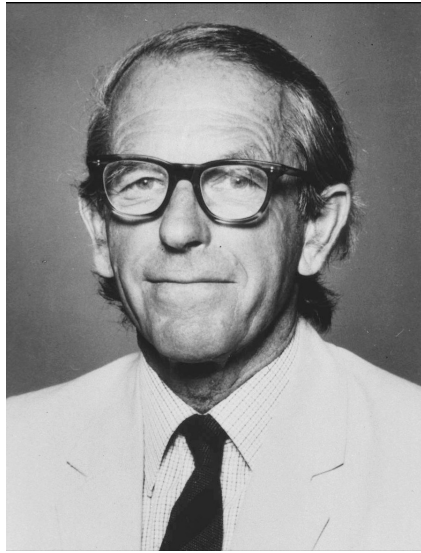
Tamsin J. Robb<sup>1,2</sup>, Peter Tsai<sup>1,2</sup>, Sandra Fitzgerald<sup>1,2</sup>, Paula Shields<sup>1</sup>, Pascalene S. Houseman<sup>1</sup>, Rachna Patel<sup>1</sup>, Vicky Fan<sup>1</sup>, Ben Curran<sup>1</sup>, Rexson Tse<sup>1,3</sup>, Jacklyn Ting<sup>4</sup>, Nicole Kramer<sup>5</sup>, Braden J. Woodhouse<sup>6</sup>, Esther Coats<sup>6</sup>, Polona Le Quesne Stabej<sup>1</sup>, Jane Reeve<sup>7</sup>, Kate Parker<sup>8</sup>, Ben Lawrence<sup>2,6</sup>, Cherie Blenkiron<sup>1,2,8</sup>, and Cristin G. Print<sup>1,2</sup>



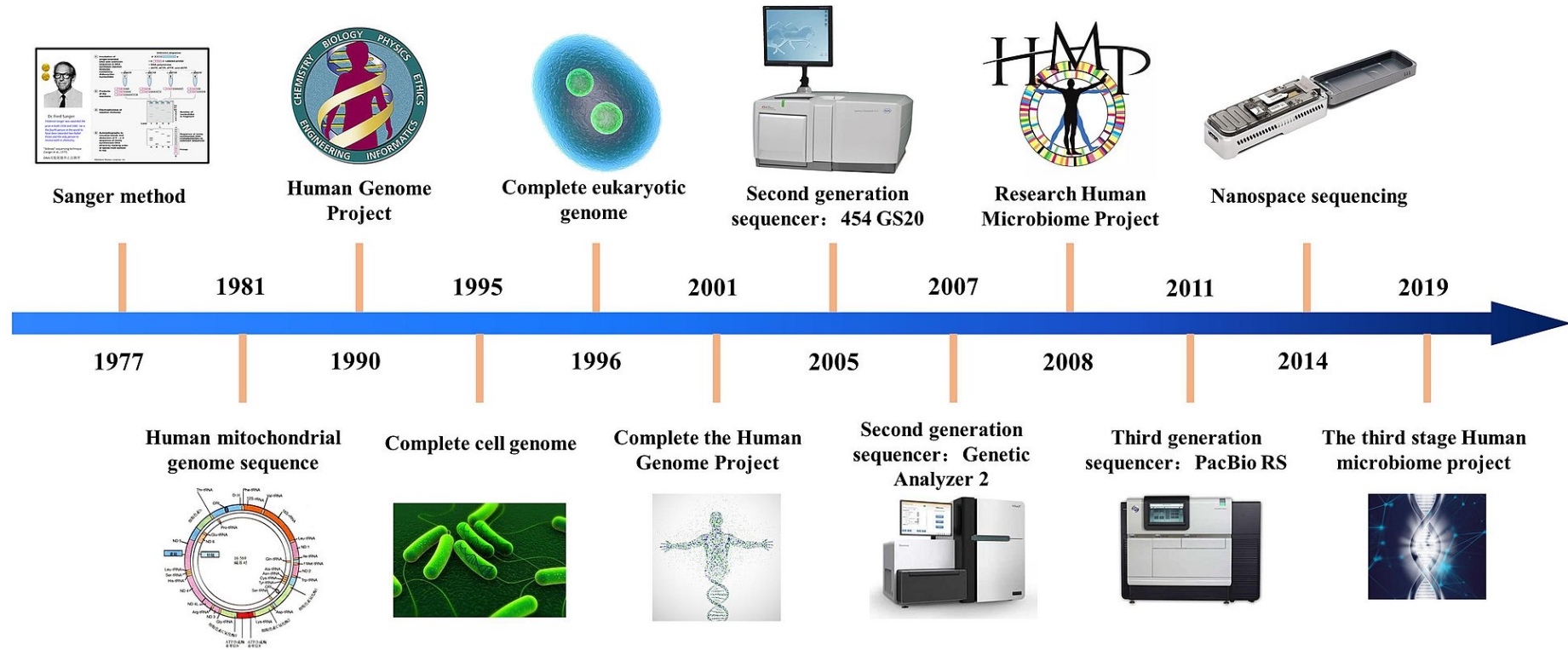
Tamsin Robb

# The start of DNA sequencing technology

# 1977



Frederick Sanger - awarded two Nobel prizes, one for the sequencing of proteins, the other for the sequencing DNA





1997

# WANTED

## 20 Volunteers

to participate in the  
**Human Genome Project**  
a very large international scientific research effort.

The goal is to decode the human hereditary information (*human blueprint*) that determines all individual traits inherited from parents. The outcome of the project will have tremendous impact on future progress of medical science and lead to improved diagnosis and treatment of hereditary diseases.

Volunteers will receive information about the project from the Clinical Genetics Service at Roswell Park, and sign a consent form before participating.

*No personal information will be maintained or transferred.*

Volunteers will provide a one-time donation of a small blood specimen. A small monetary reimbursement will be provided to the participants for their time and effort.

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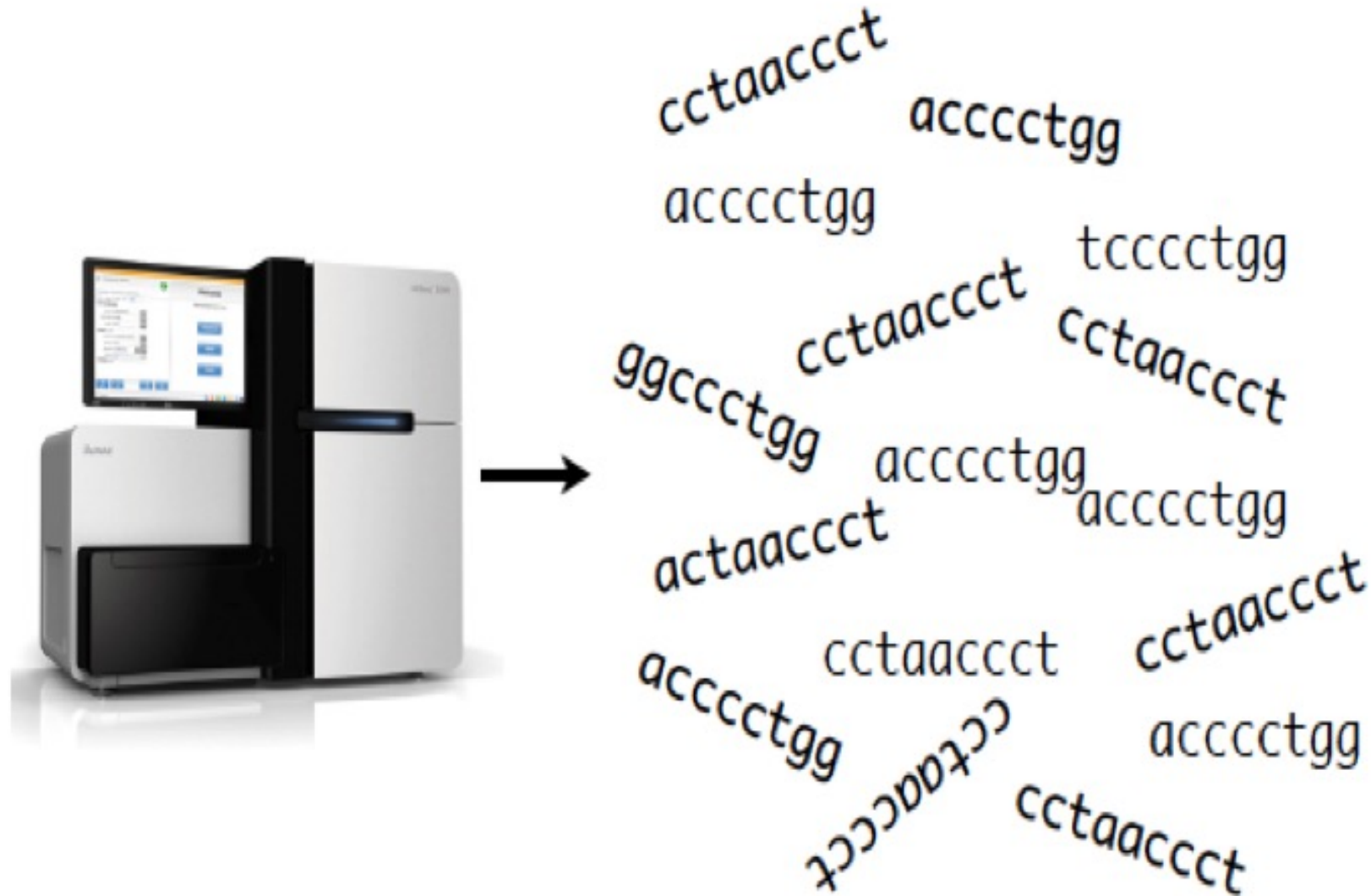
Individuals must be at least 18 years of age.  
Persons who have undergone chemotherapy are not eligible.



For more information please contact the  
Clinical Genetics Service  
845-5720 (9:00 am - 3:00 pm)  
March 24 - 26, 1997

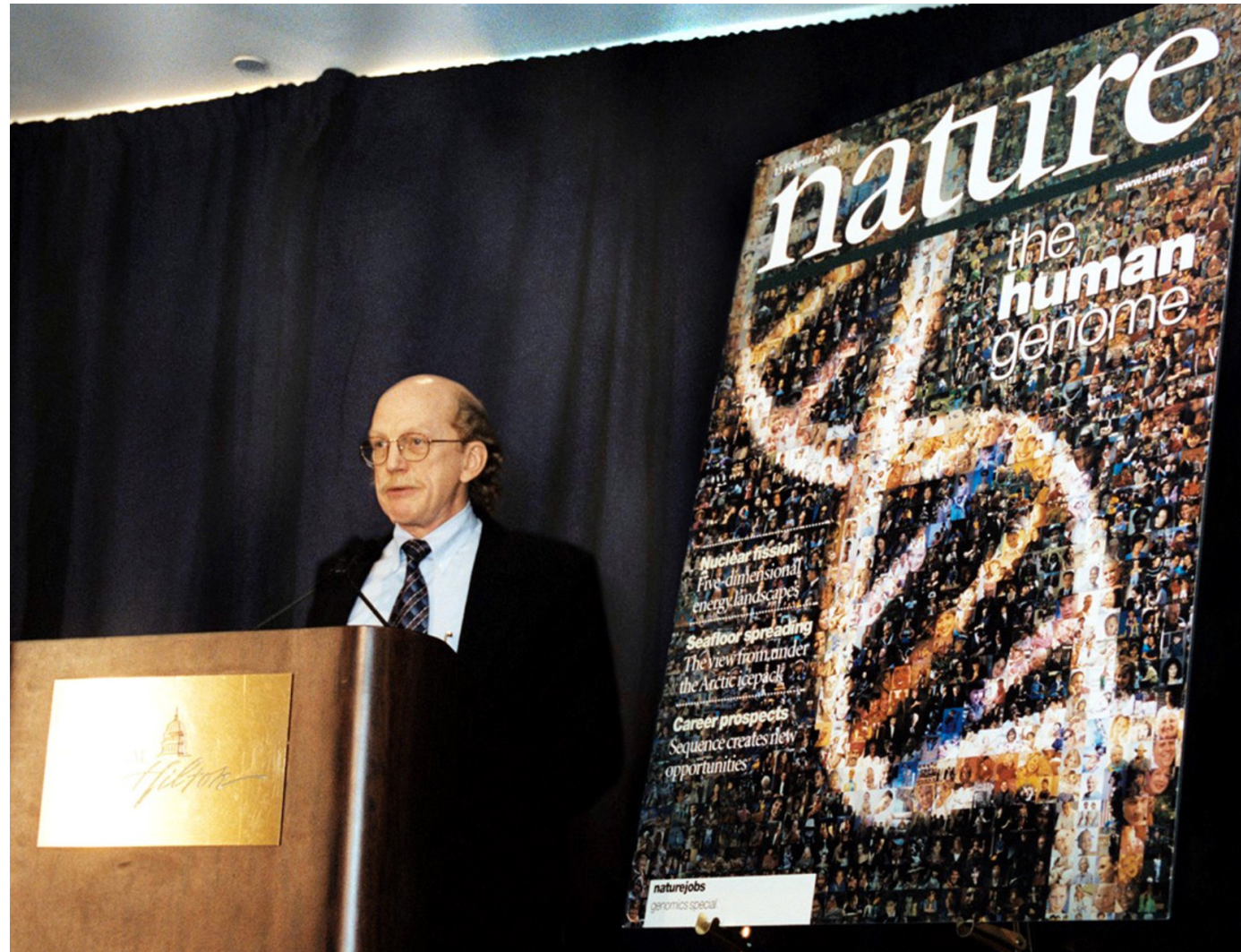
# “Next Generation” Sequencing

1998





# Robert Waterson, at the 2001 press conference announcing the publication of the draft sequence of the human genome

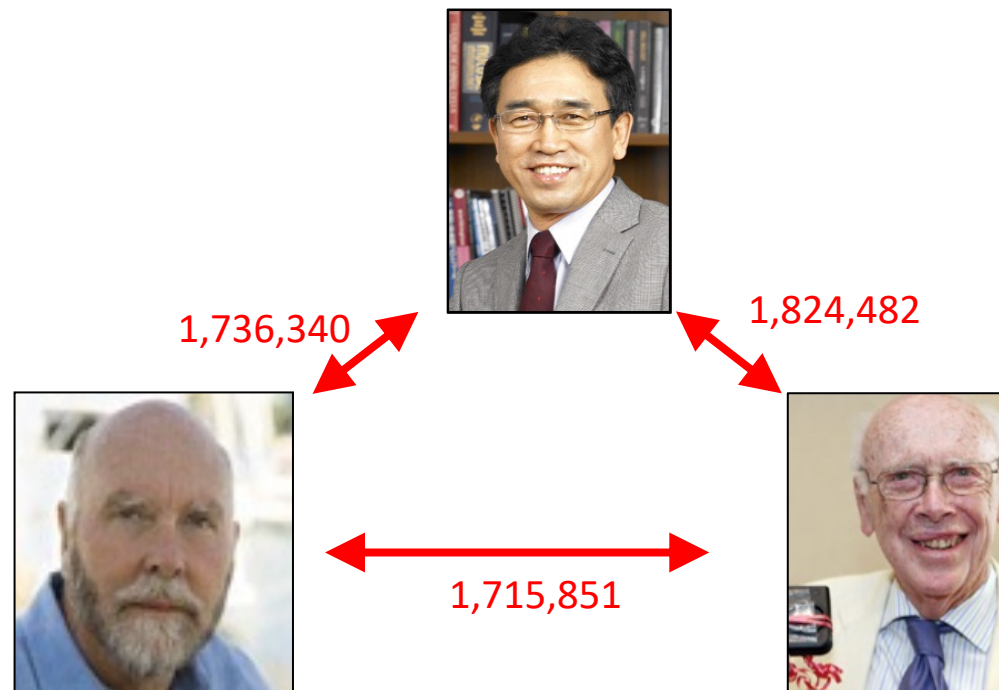


<https://www.genome.gov/about-genomics/educational-resources/fact-sheets/human-genome-project>

# Sequencing of Individual Humans

2008

- The first three *individual* humans had their DNA sequenced in 2007-2009
- Craig Venter, James Watson and Seong-Jin Kim



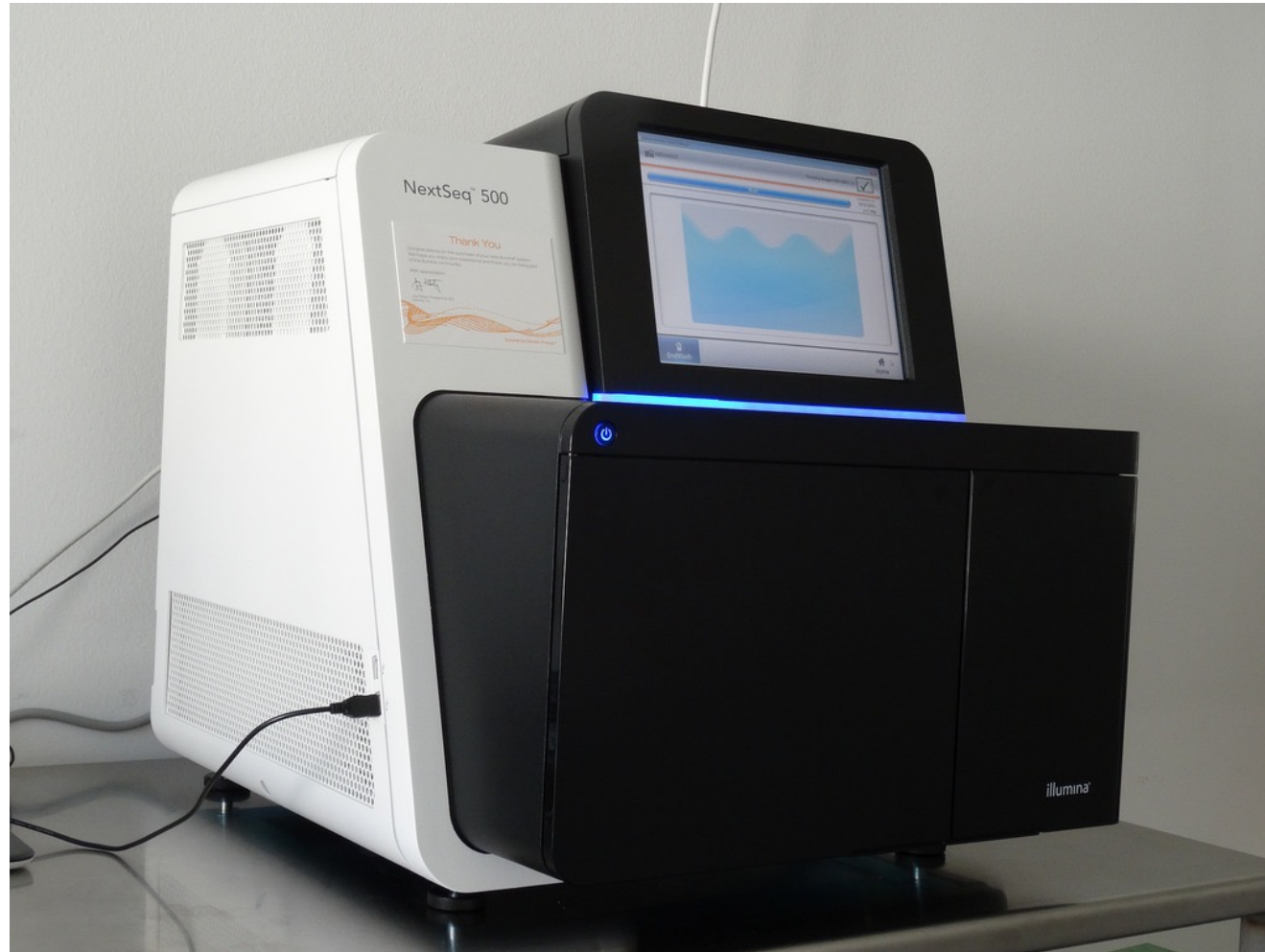
Barbujani and Pigliucci  
2013, Current Biology 23  
R185–R187



# The relentless advance of DNA sequencing technology



# The relentless advance of DNA sequencing technology



# The relentless advance of DNA sequencing technology



# Cost per Human Genome



**NIH** National Human Genome Research Institute

[genome.gov/sequencingcosts](https://genome.gov/sequencingcosts)



# Spontaneous somatic mutations occur in normal tissues and non-cancer conditions

2015



JNCI J Natl Cancer Inst (2016) 108(8): djw036

doi: 10.1093/jnci/djw036

First published online April 7, 2016

Review

REVIEW

## The Conundrum of Genetic “Drivers” in Benign Conditions

Shumei Kato\*, Scott M. Lippman\*, Keith T. Flaherty, Razelle Kurzrock

**Affiliations of authors:** Department of Investigational Cancer Therapeutics, MD Anderson Cancer Center, Houston, TX (SK); Center for Personalized Cancer Therapy and Division of Hematology and Oncology, UC San Diego Moores Cancer Center, La Jolla, CA (SML, RK); Henri and Belinda Termeer Center for Targeted Therapies, Massachusetts General Hospital Cancer Center, Boston, MA (KTF)

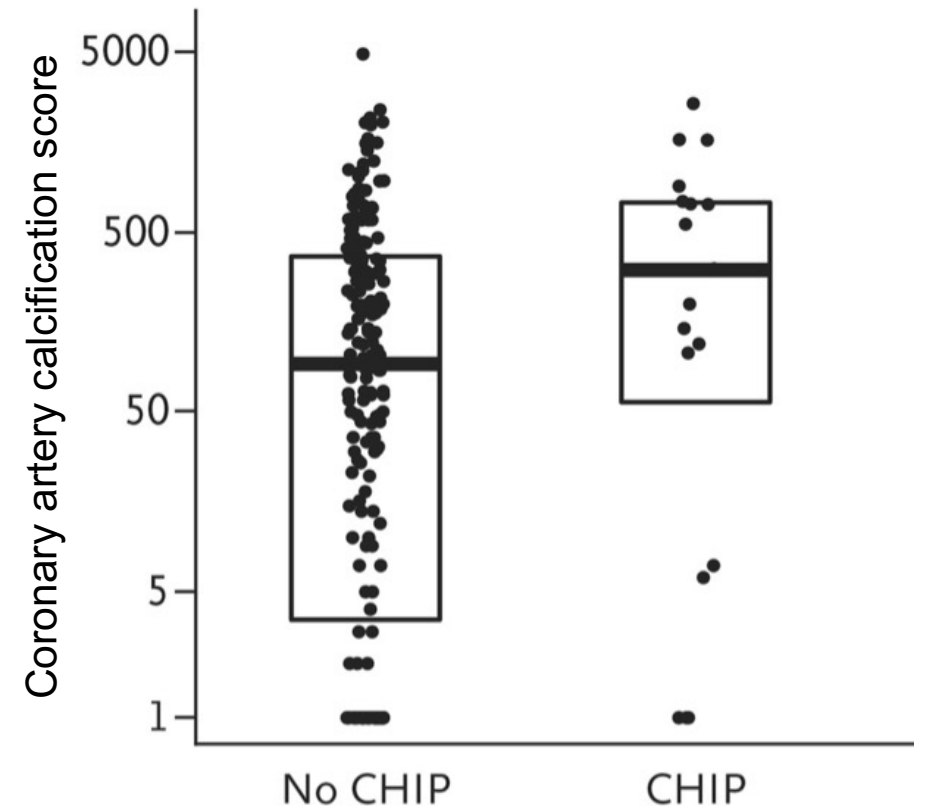
\*Authors contributed equally to this work.

Potentially these mutations are generated by:

- Replicative aging & cell turnover in tissue
- Oxidative stress
- Inflammation
- Chemical or radiological mutagens ...

# Clonal haematopoiesis of indeterminate potential (CHIP)

- CHIP is a blood stem cell “clone” carrying a somatic mutation in patients with no other haematological abnormality
- Accumulates with age (found in >10% of people >70 years)
- Commonly mutated genes are: *DNMT3A*, *TET2*, *JAK2*, *ASXL1*
- Case–control analyses showed that CHIP carriers have ~ 2 x elevated risk of coronary heart disease

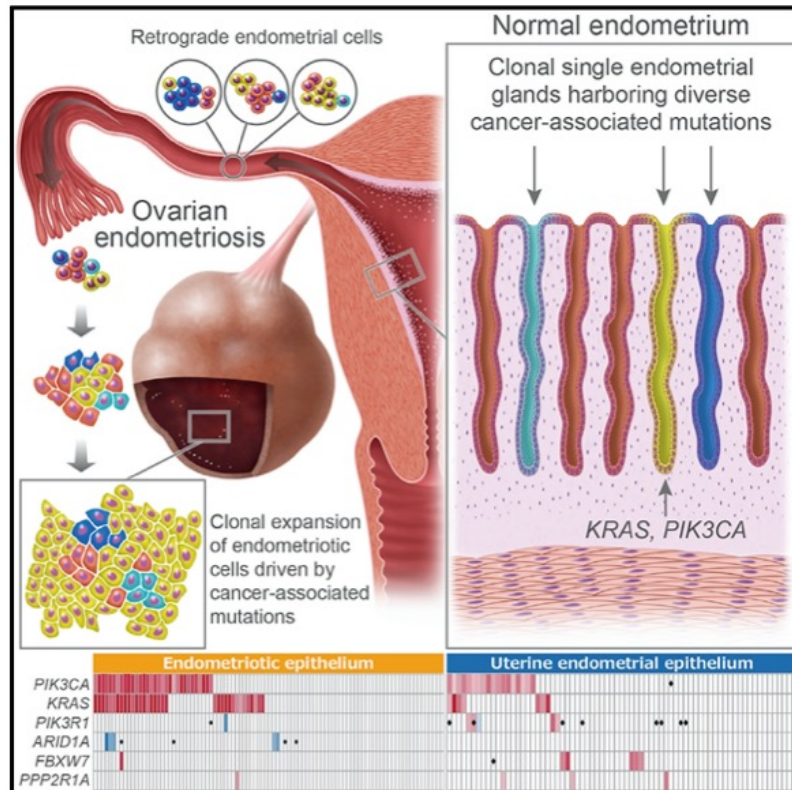




# Spontaneous somatic mutations occur in normal tissues and non-cancer conditions

## Clonal Expansion and Diversification of Cancer-Associated Mutations in Endometriosis and Normal Endometrium

### Graphical Abstract



### Authors

Kazuaki Suda, Hirofumi Nakaoka, Kosuke Yoshihara, ..., Teiichi Motoyama, Ituro Inoue, Takayuki Enomoto

### Correspondence

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itinoue@nig.ac.jp (I.I.),  
enomoto@med.niigata-u.ac.jp (T.E.)

### In Brief

Suda et al. identify numerous cancer-associated mutations in epithelial cells from ovarian endometriosis and normal endometrium. They describe a heterogeneous and mosaic-like uterine endometrial epithelium, shaped by endometrial glands with distinct somatic mutations. They suggest clonal expansion of epithelial cells with cancer-associated mutations leads to the development of endometriosis.

- Distinct mutations in individual endometrial glands → clonal expansion
- Genetically heterogeneous 'clumps' of retrogradely menstruated endometrium

SCIENCE / HEALTH

# Cracking the final piece of the human genome puzzle

From [The Detail](#), 5:00 am on 13 April 2022

Share this

[Alexia Russell](#), reporter for The Detail[alexia.russell@rnz.co.nz](mailto:alexia.russell@rnz.co.nz)

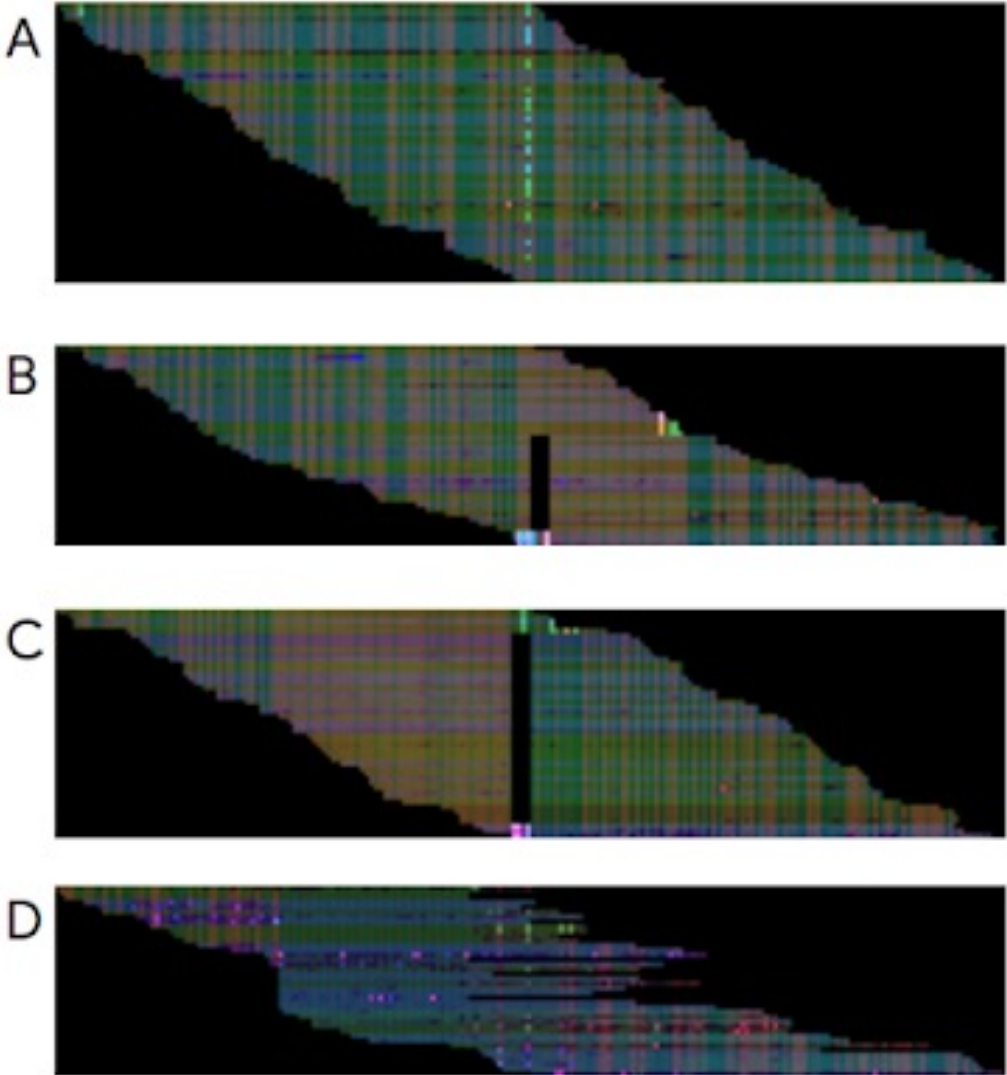
Output from a DNA sequencer. Photo: National Human Genome Research Institute

*It's taken thousands of scientists decades to finish mapping the human genome. The Detail looks at why it's taken so long and what it might mean for indigenous populations here in Aotearoa and around the world.*





# Machine Learning and AI are already critical research analysis tools



DeepVariant

Model: GPT-4

**c** Write me a snakemake pipeline to do: fastqc quality control, read trimming, bwa -mem alignment, sort, mark duplicates, index and samtool flag stat for 32 whole genome sequence fastq files using a 40 core unix server

Below is a Snakemake pipeline to perform the tasks you mentioned for 32 whole genome sequence fastq files using a 40-core UNIX server. 📄 👍 🗨️

1. Install Snakemake on your server if you haven't already:

```
conda create -n snakemake-env -c conda-forge -c bioconda snakemake-minimal
conda activate snakemake-env
```

2. Create a `Snakefile` in your working directory and paste the following code:

```
python
SAMPLES = [f"sample{i}" for i in range(1, 33)]
THREADS = 40

rule all:
    input:
        expand("aligned/{sample}.flagstat", sample=SAMPLES)

rule fastqc:
    input:
        r1="raw_data/{sample}_R1.fastq.gz"
        r2="raw_data/{sample}_R2.fastq.gz"
```

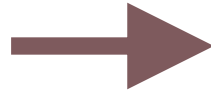
🔄 Regenerate response

Send a message...

ChatGTP

# Why do these technologies matter?

They matter because these advances in technology open a wider window onto disease biology

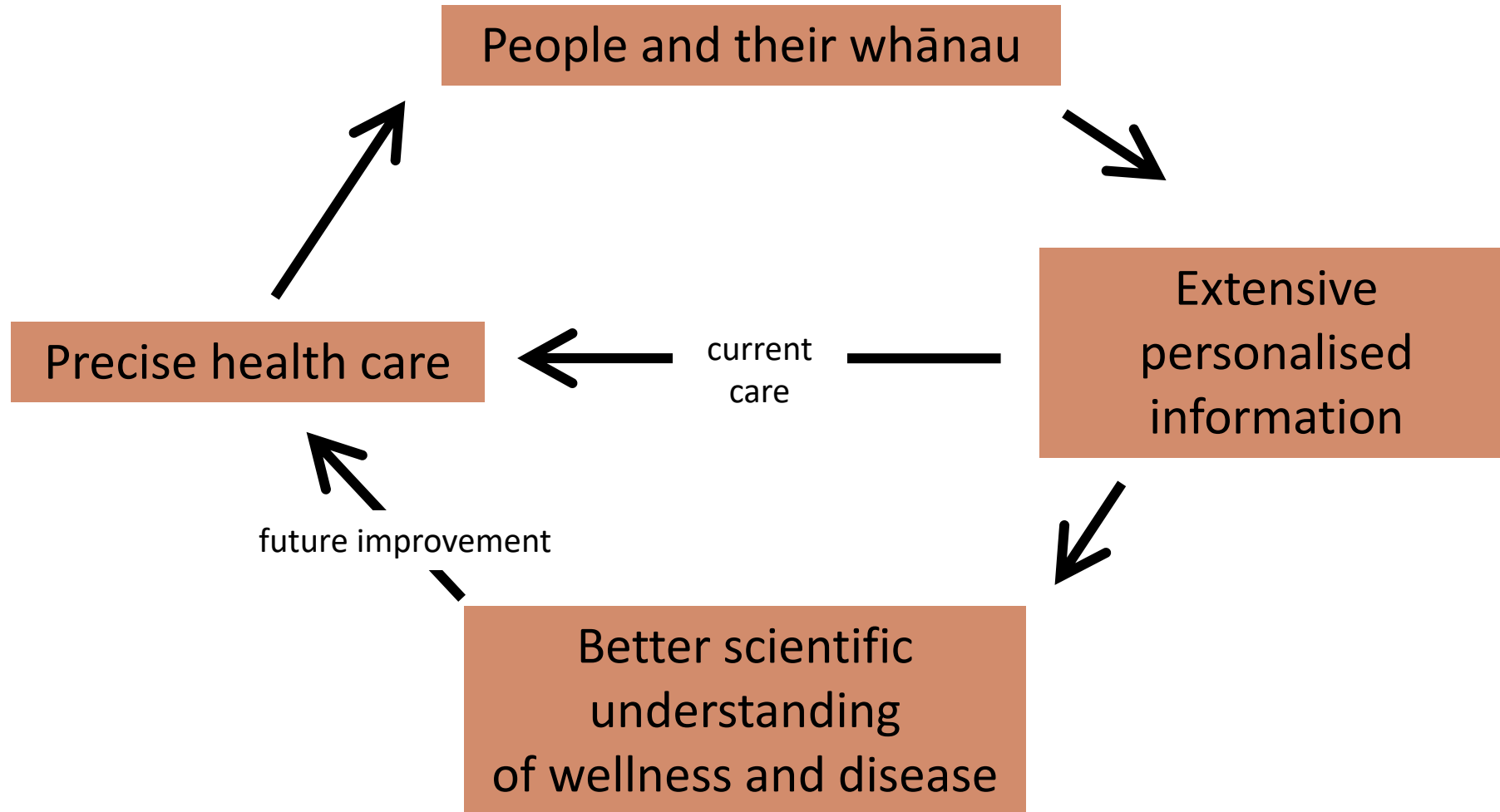


- Increased impact on current patient care
- Increased potential for today's biobank-enabled research to enhance future patient care

# Applying these technologies for patients



# Precision Medicine's Clinical Delivery is Intimately Intertwined with Research

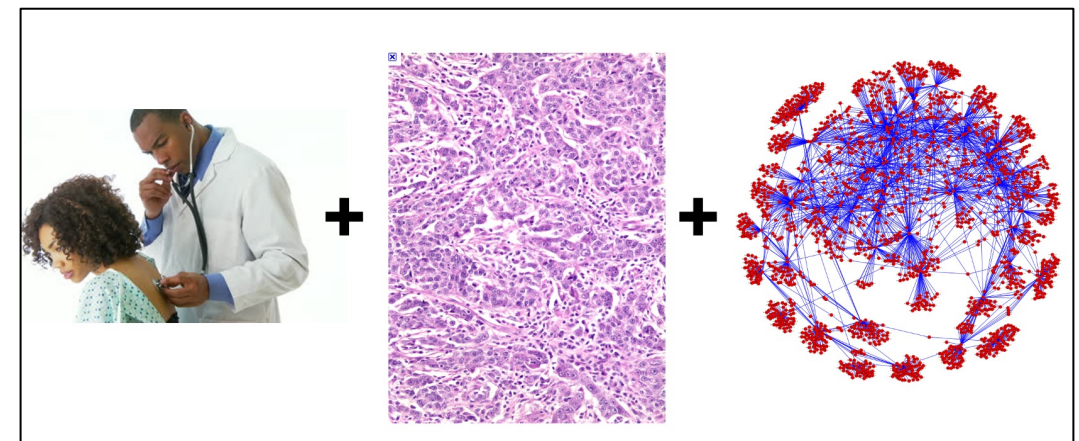




# Eric Topol's NHS review – teams with new skills...



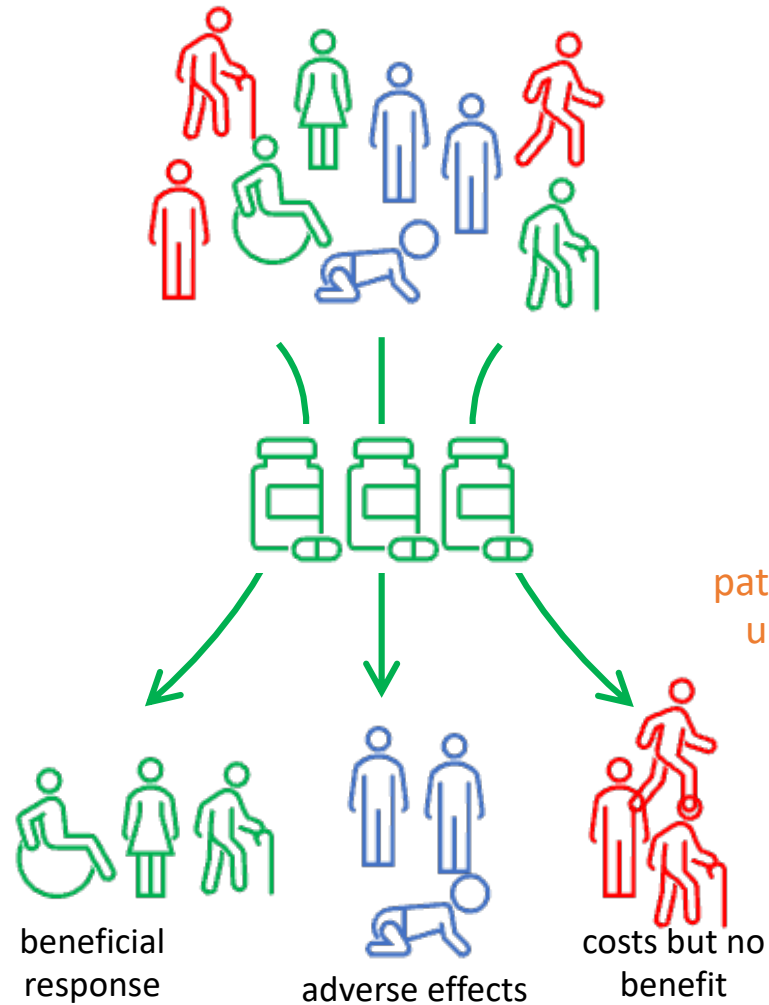
- “Within 20 years, 90% of all jobs in the NHS will require some element of digital skills”
- “All staff will need digital and genomics literacy”



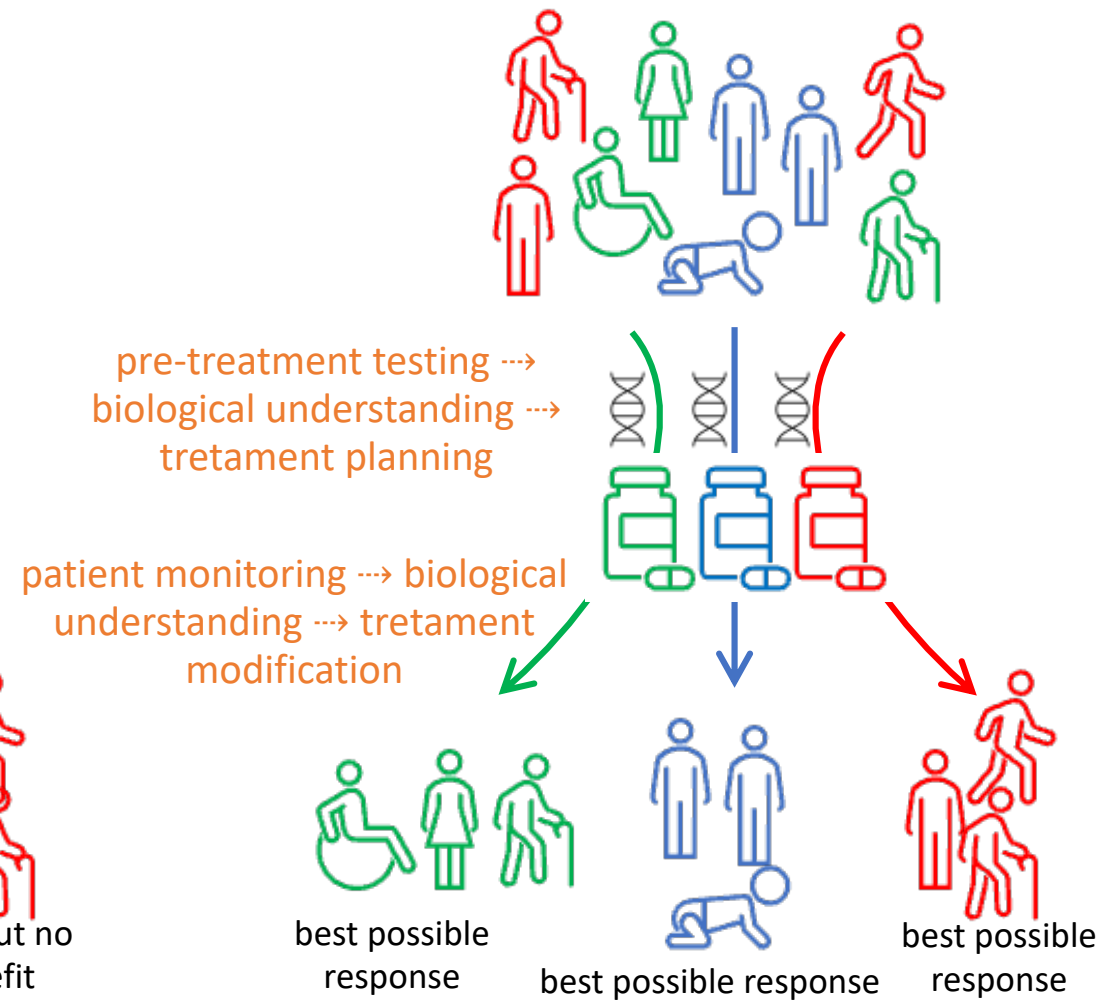


# The concept of Precision Medicine

(A) The same treatment for all



(B) Biomarker-guided individualised treatment



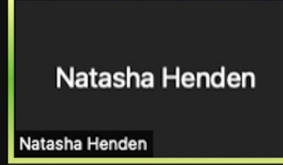
# Genomics examples



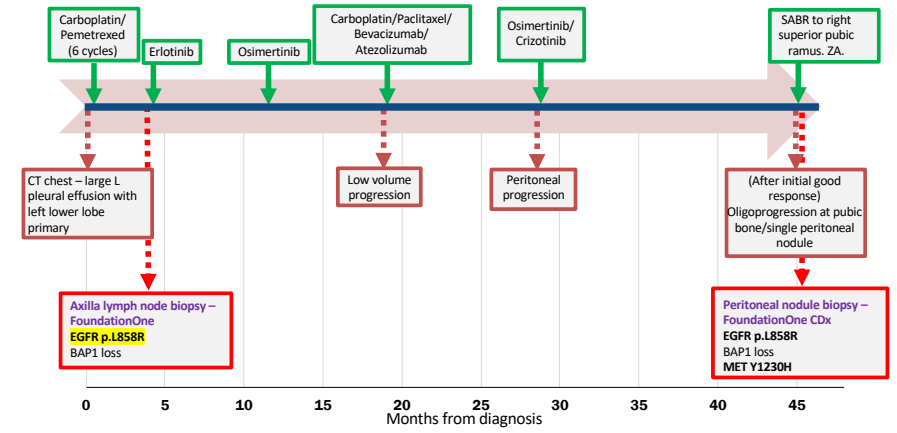
# Molecular Tumour Boards: Team-based Clinical Decisions

82yo, female  
Pancreatic carcinoma

	<b>STK11</b> p.E57fs*8	<b>STK11</b> p.L282fs*3	<b>CDKN2A/B:</b> p16(INK4A): A68fs*51 p14(ARF): G83fs*77
<b>Population Databases</b> GnomAD	Not present	<b>NFE:</b> 1 heterozygote (9.185E-6)	Not present
<b>Somatic Databases</b> COSMIC, ONKOKb, Cancer HotSpot	Not present <small>COSMIC: STK11 LoF variants detected in 1.81% of pancreatic cancer cohort.</small>	COSMIC: 12x observations 7x lung, 3x large intestine, 1x pancreatic, 1x cervical.	Not present <small>COSMIC: CDKN2A/B LoF variants detected in 7.64% of pancreatic cancer cohort.</small>
<b>Germline Databases</b> ClinVar, InSIGHT, LOVD	Not present	Pathogenic <small>ClinVar: 3x germline observations – HCS, Peutz-Jeghers syndrome.</small>	Not present
<b>Literature</b> MasterMind	Not reported <small>STK11 mutations frequently co-occur with KRAS mutations (NSCLC)</small>	Reported in 6 families with Peutz-Jaghers syndrome (10-35% cancer risk of Pancreatic cancer)	Not reported <small>CDKN2A germline variants associated with familial melanoma, pancreatic ca, HNSCC.</small>
<b>Somatic/Germline?</b>	Suspected somatic	Suspected somatic	Unknown <small>Referral to GHS recommended due to Phx and Fhx: known germline association</small>
<b>Pathogenicity</b>	Likely pathogenic PVS1 + PM2	Pathogenic PVS1 + PS4_SUPP + PM2	Likely pathogenic PVS1 + PM2



- AM
- BL
- CW
- e
- E
- EW
- KS
- LR
- N
- OP
- O
- PF
- PL



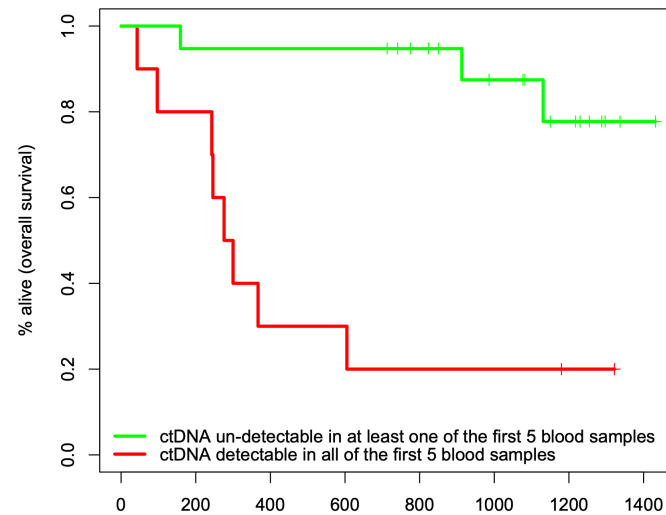
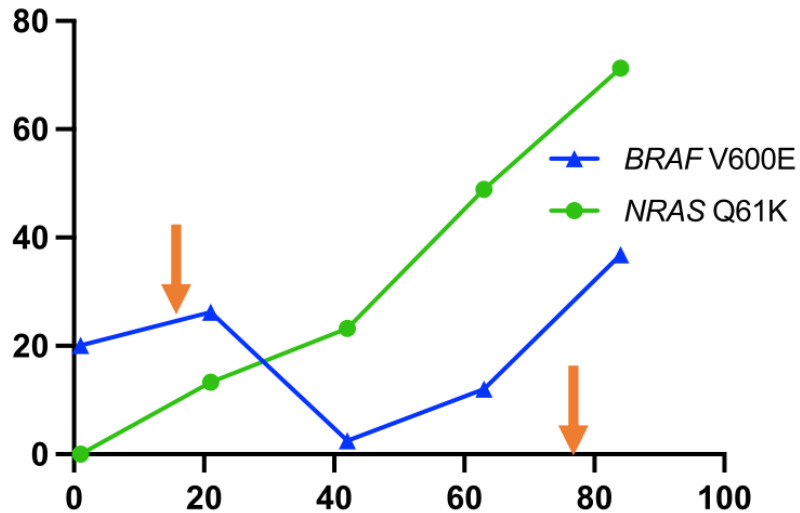
# The Auckland Molecular Screening and Therapeutics (MoST) program

- Opened in Auckland in 2022, adapting the master protocol to the needs of the NZ population
- Has recruited over 200 participants, over-recruiting Māori and Pacific people
- A potential platform for future decentralised trials



Michelle Wilson  
Ben Lawrence

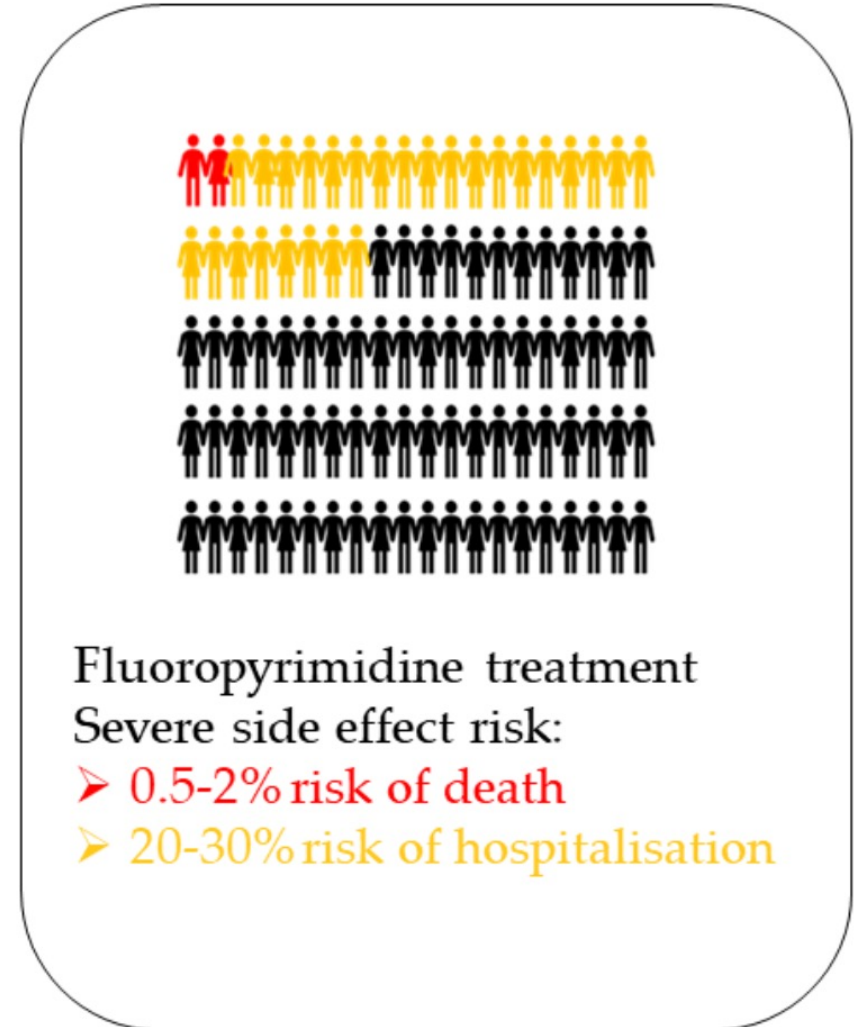
# Gene sequencing of blood tests identifies the 'evolution' of multiple metastatic tumours over time



Sandra Fitzgerald  
Parry Guilford

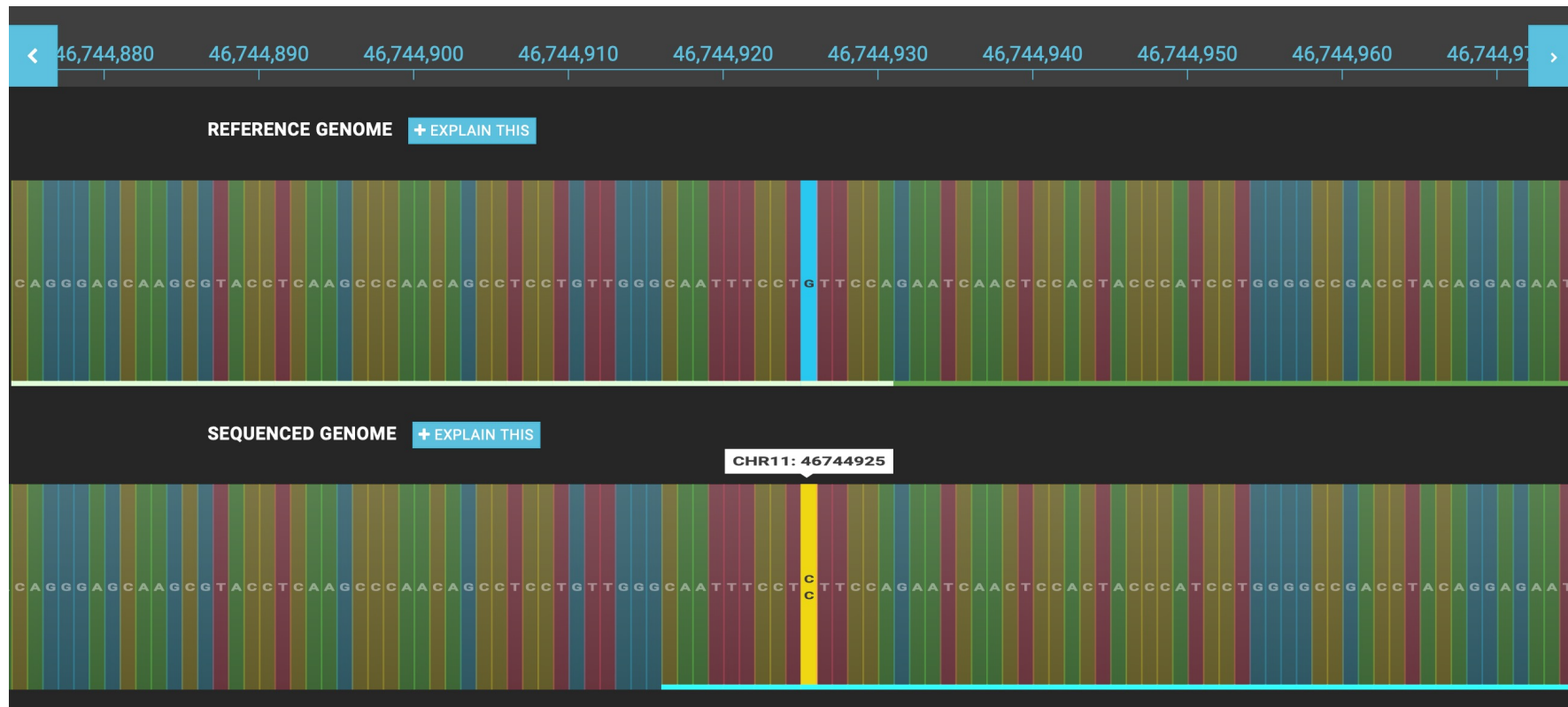
# A 'pharmacogenomics' example

- About 2% of people have a set of specific differences in their *DYPD* gene
- If you have these differences and receive the common oncology drug 5-Flourouracil (5-FU), you have ~ 70% likelihood of toxicity
- In NZ ~ 1,500 patients per year receive 5-FU
- About 30 of these patients will have these *DYPD* differences, leading to ~20 NZ patients each year developing severe toxicity
- An inexpensive genomic test can determine these *DYPD* differences, allowing medical oncologists to reduce the 5-FU toxicity



# A personal example

- My own whole genome sequencing found a difference in my prothrombin gene that slightly increases my chance of deep venous thrombosis and pulmonary embolism
- I also have a family history of these disorders, therefore I take preventative measures

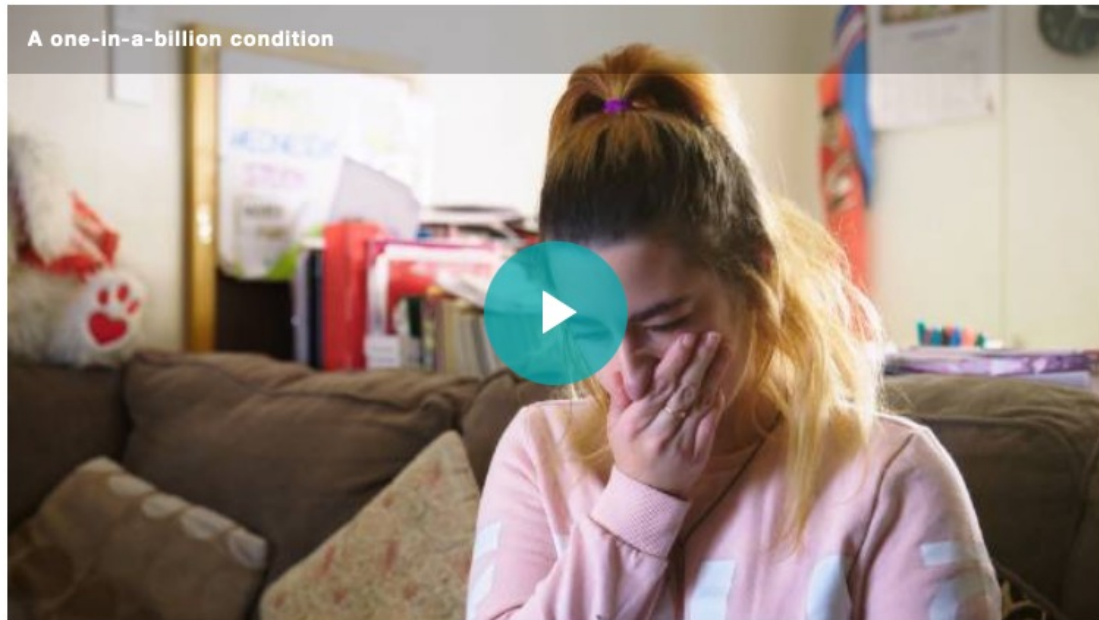




# Genomics has impact outside of cancer of course

## An answer at last for Kiwi siblings coping with one-in-a-billion condition

Aotearoa Science Agency • 11:57, Sep 09 2018



SUPPLIED

Rebecca and her brother Arthur have a one-in-a-billion condition.

JOURNAL OF THE ROYAL SOCIETY OF NEW ZEALAND  
<https://doi.org/10.1080/03036758.2018.1464033>



RESEARCH ARTICLE



### A pilot study of exome sequencing in a diverse New Zealand cohort with undiagnosed disorders and cancer

Colina McKeown<sup>a</sup>, Samantha Connors<sup>b</sup>, Rachel Stapleton<sup>b,a</sup>, Tim Morgan<sup>b</sup>, Ian Hayes<sup>c</sup>, Katherine Neas<sup>a</sup>, Joanne Dixon<sup>d</sup>, Kate Gibson<sup>d</sup>, David M. Markie<sup>b,b</sup>, Peter Tsai<sup>e</sup>, Cherie Blenkiron<sup>b,e</sup>, Sandra Fitzgerald<sup>e</sup>, Paula Shields<sup>e</sup>, Patrick Yap<sup>c</sup>, Ben Lawrence<sup>e</sup>, Cristin Print<sup>b,e</sup> and Stephen P. Robertson<sup>b,b,d</sup>

<sup>a</sup>Genetic Health Service New Zealand, Wellington Hospital, Wellington, New Zealand; <sup>b</sup>Dunedin School of Medicine, University of Otago, Dunedin, New Zealand; <sup>c</sup>Genetic Health Service New Zealand, Auckland Hospital, Auckland, New Zealand; <sup>d</sup>Genetic Health Service New Zealand, Christchurch Hospital, Christchurch, New Zealand; <sup>e</sup>School of Medical Sciences and Maurice Wilkins Centre, University of Auckland, Auckland, New Zealand

#### ABSTRACT

We report the results of a pilot project for clinical DNA sequencing in New Zealand. This project aimed to estimate the diagnostic yield of next generation sequencing in the New Zealand clinical environment. Trio whole exome sequencing (WES) was performed on germline DNA of 40 individuals from 12 families with presumptive Mendelian disorders. In addition, both WES and deep targeted sequencing (DTS) was performed on tumours, metastases and corresponding normal blood leukocytes from two cancer patients. For the rare Mendelian disorder cohort, the diagnostic yield was 6/12, including previously recognised pathogenic mutations and novel mutations. In tumour sequence analysis, WES identified somatic single nucleotide mutations and copy number aberrations in both cancer patients; however, DTS was required to obtain clinically informative information. This study showed that diagnostic germline and tumour WES and DTS could be easily undertaken in New Zealand, and identified specific infrastructural challenges that must be solved to facilitate its clinical use.

#### ARTICLE HISTORY

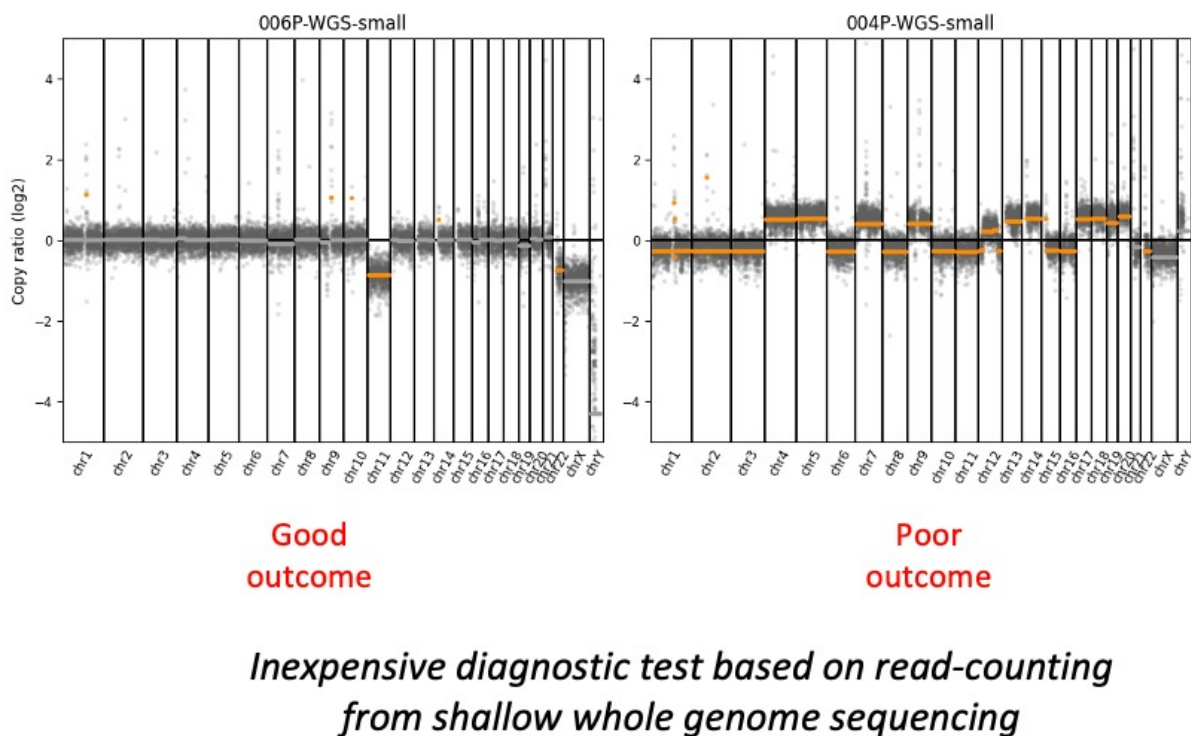
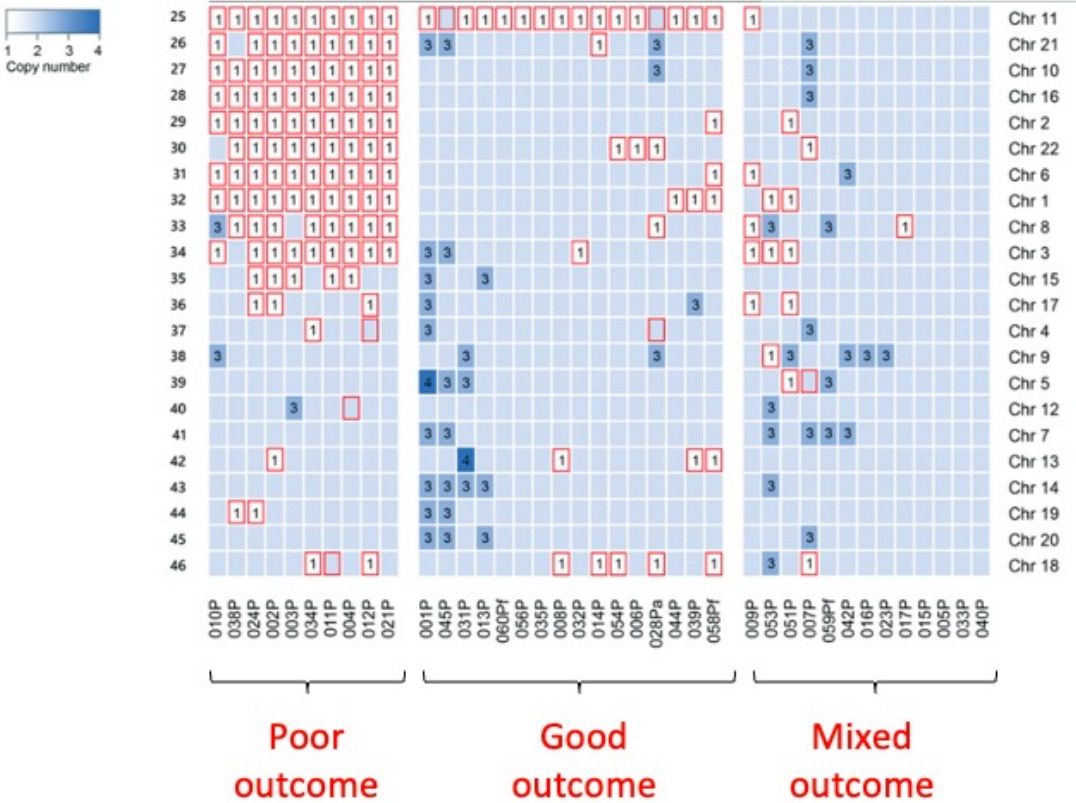
Received 24 January 2018  
Accepted 10 April 2018

#### KEYWORDS

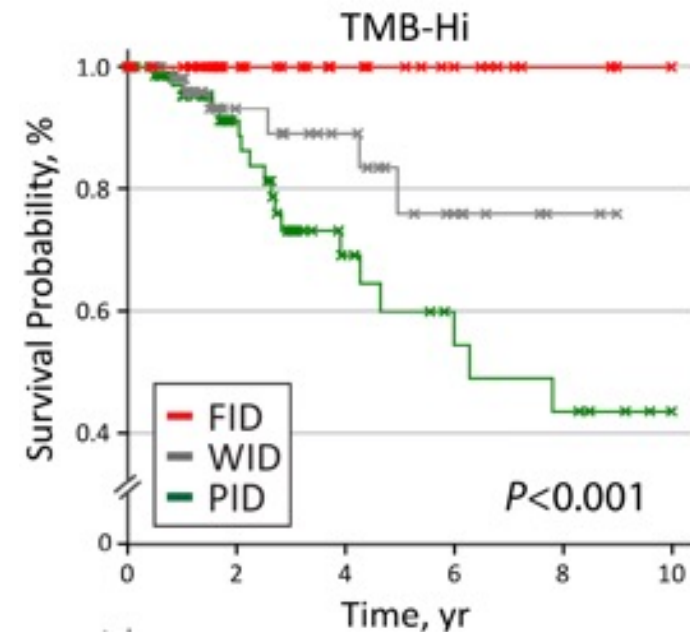
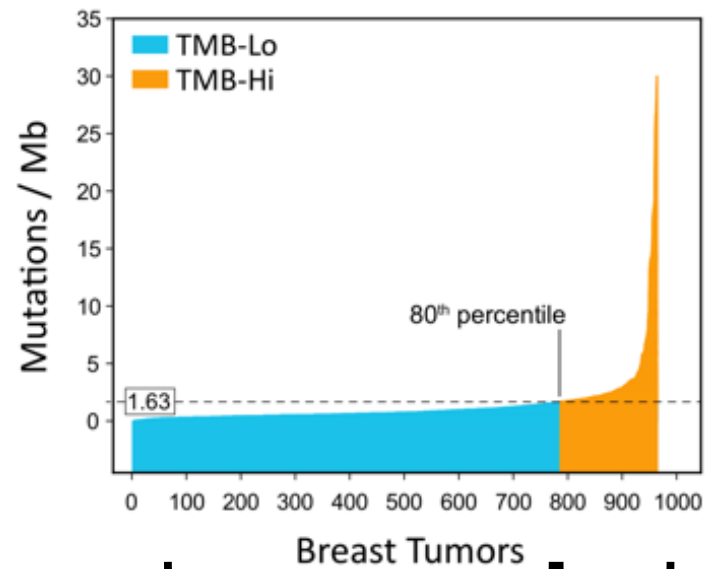
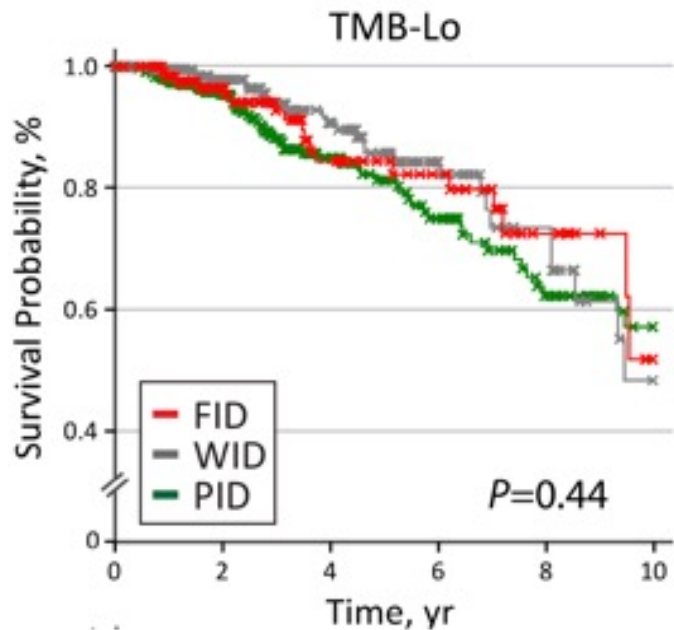
Clinical genetics; New Zealand; rare disease; whole exome sequencing; diagnostic cancer genomics



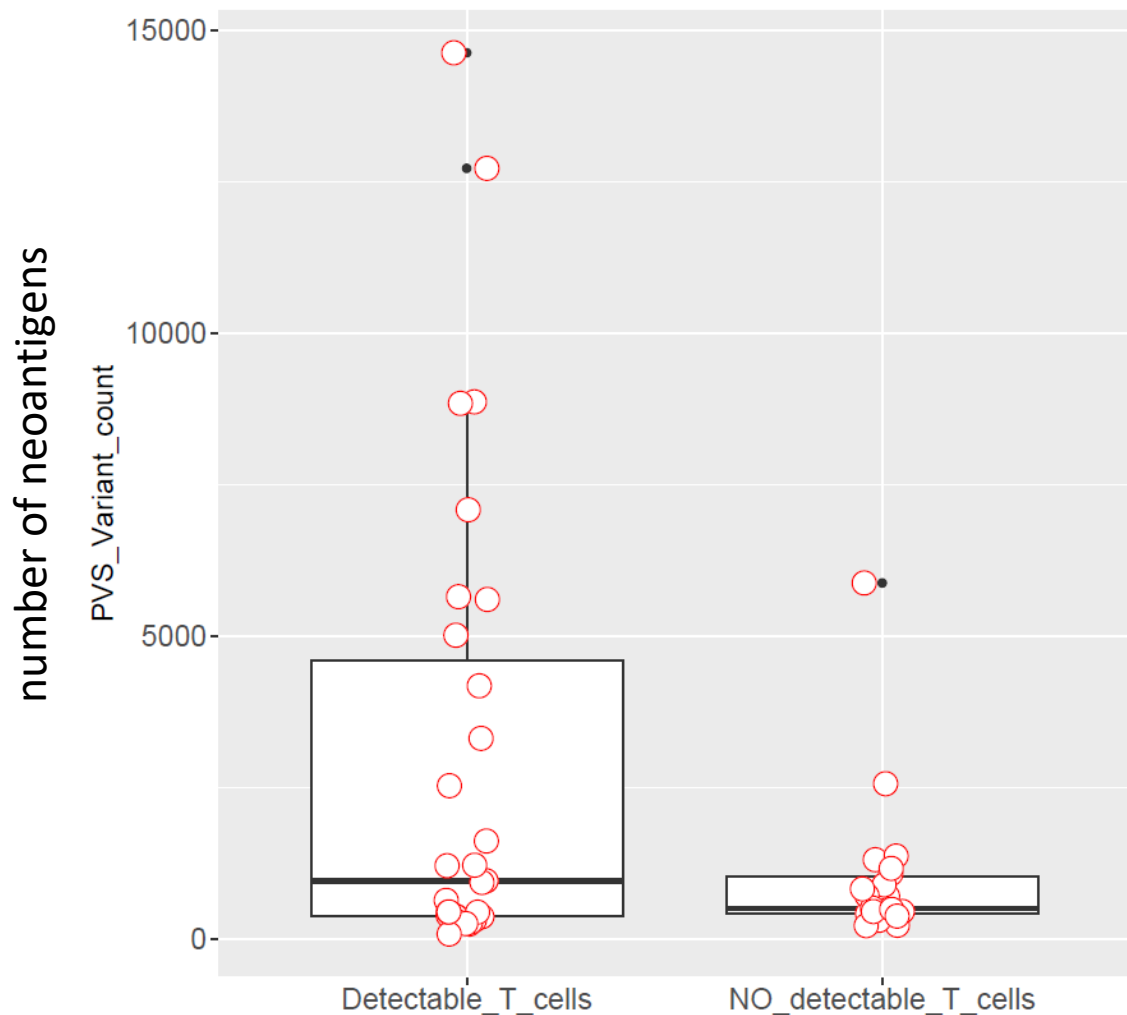
# Surgical biomarker example: Gene sequencing to identify those patients with pancreatic neuroendocrine tumours who may not require aggressive surgery



# Genomics providing a window into Tumour Immunology



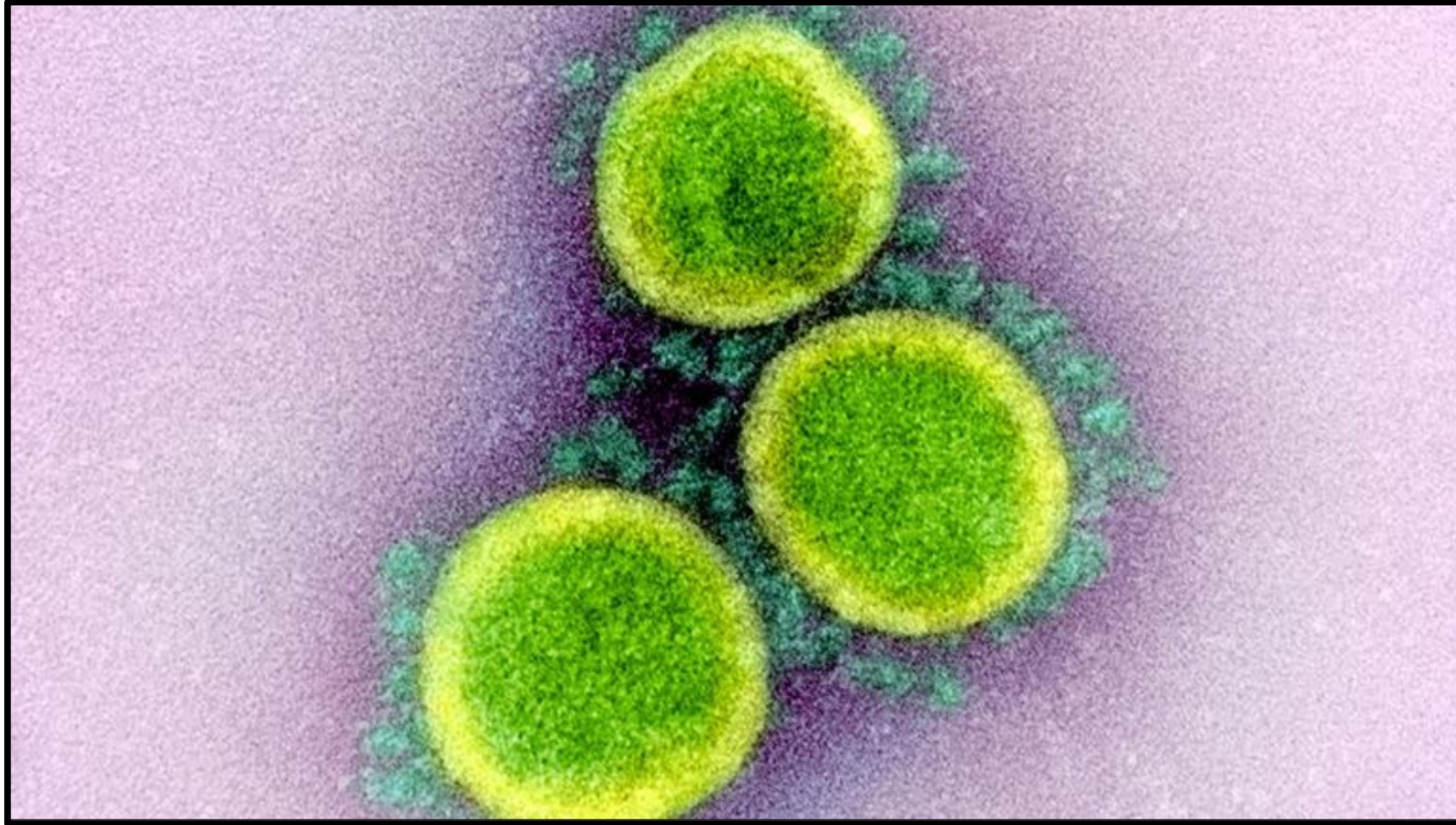
# Genomics providing a window into Endometriosis Immunology



- Identify 'presentable' somatic mutations, given each patient's HLA haplotype, using GATK RNA variant calling pipeline
- Infer T cell infiltration using 'Cibersort'



# SARS-CoV-2 genomics in the COVID-19 pandemic



**Where to now?**





## **Te pae tika:**

e tūhura ana i ngā ara hou me ngā ārai ki te āta matapaetanga, te kauparenga atu, te kitenga me te rongoātanga o ngā take hauora ki Aotearoa

## **Precision health:**

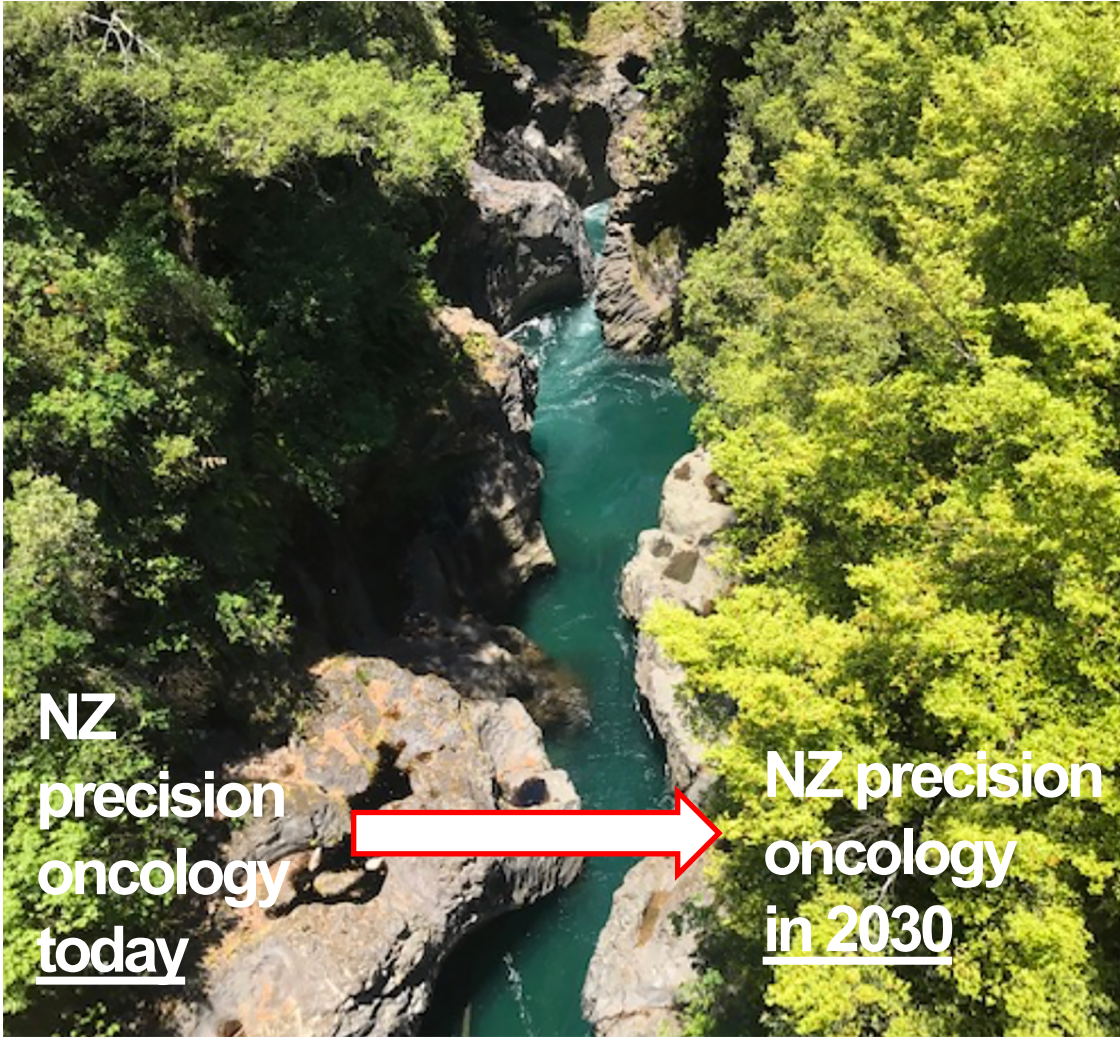
exploring opportunities and challenges to predict, prevent, diagnose, and treat health needs more precisely in Aotearoa New Zealand



**Energy and focus is going into working out how to advance precision health in a relatively resource-constrained environment**

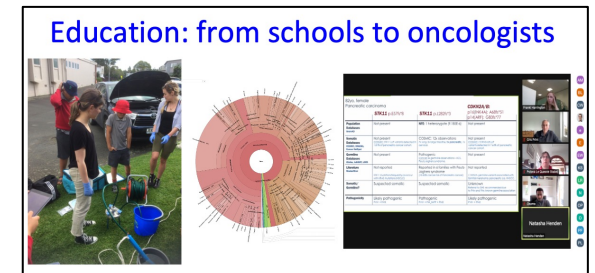


# Crossing the canyon



- What is happening currently
  - Throwing ropes across the canyon in the short-medium term to illustrate the promise
  - Making a start on some foundations for the definitive bridge
- Enablers:
  - A potentially under-treated patient population
  - Motivated clinicians, scientists, national agencies and industry
  - Close Australian partnerships (clinical and research)
  - Nationally joined-up health system and patient identifiers
  - Clarity and vision from Māori leaders in this space
  - 10+ years of work generating many of the building blocks
- Dividends:
  - Clinical (patients/families) and Scientific (understanding)
  - Equity and Economic

# Examples of local infrastructures, centres and programs

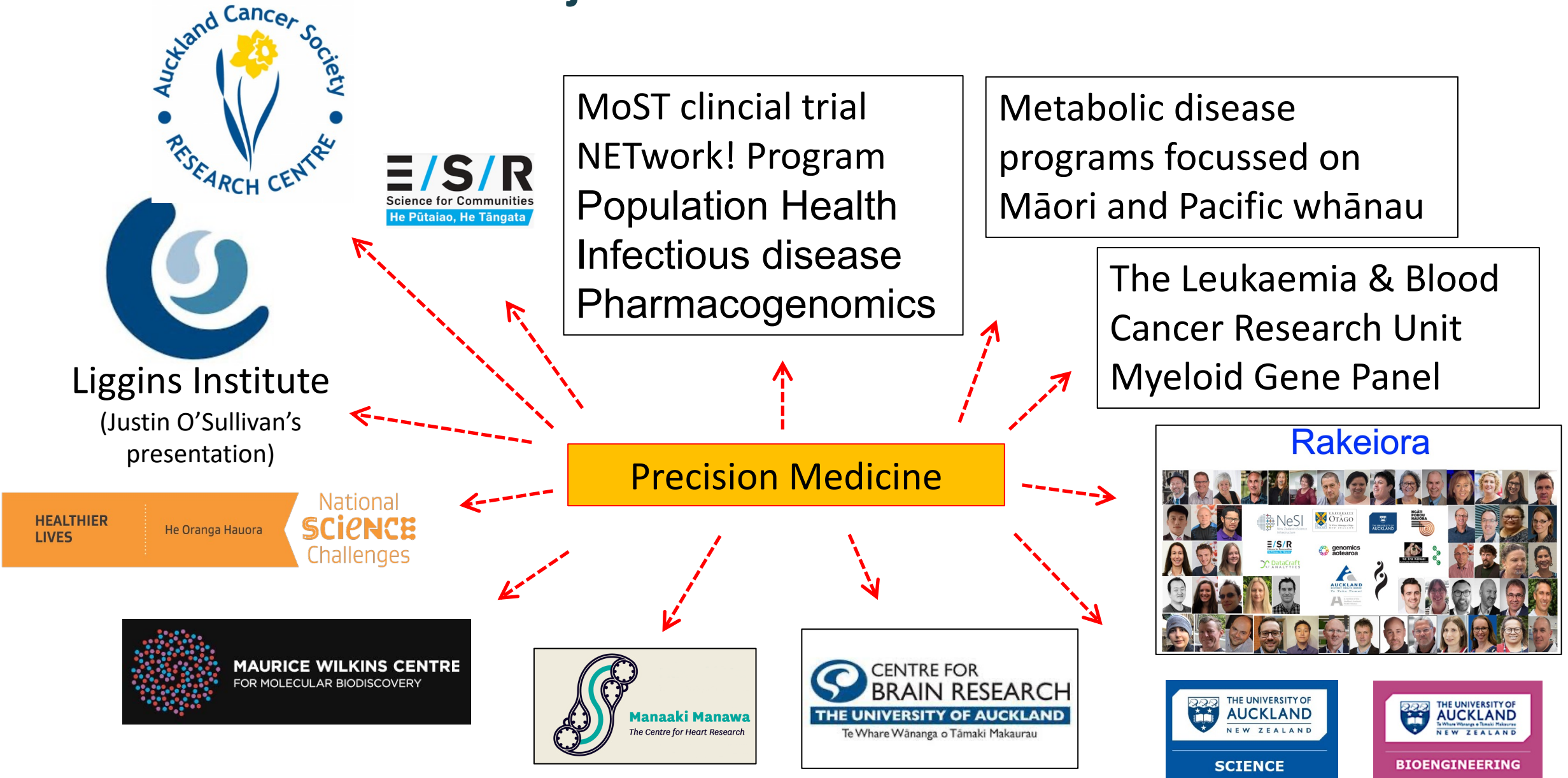


Aotearoa Genomic Healthcare Alliance





# Examples of the scope of Precision Medicine activity in Auckland: Projects and Collaborations



# Summary

- The rapid advances of genomic technologies used in today's research underpins tomorrow's clinical care
- This field really is moving at breakneck speed!
- Ongoing investment into research is needed to keep up with the clinically-relevant information these technologies produce



# E hara taku toa i te toa takitahi, engari he toa takitini

(The greatest success comes from working together)





