The impact of germline genetics on breast cancer and integration in clinical practice

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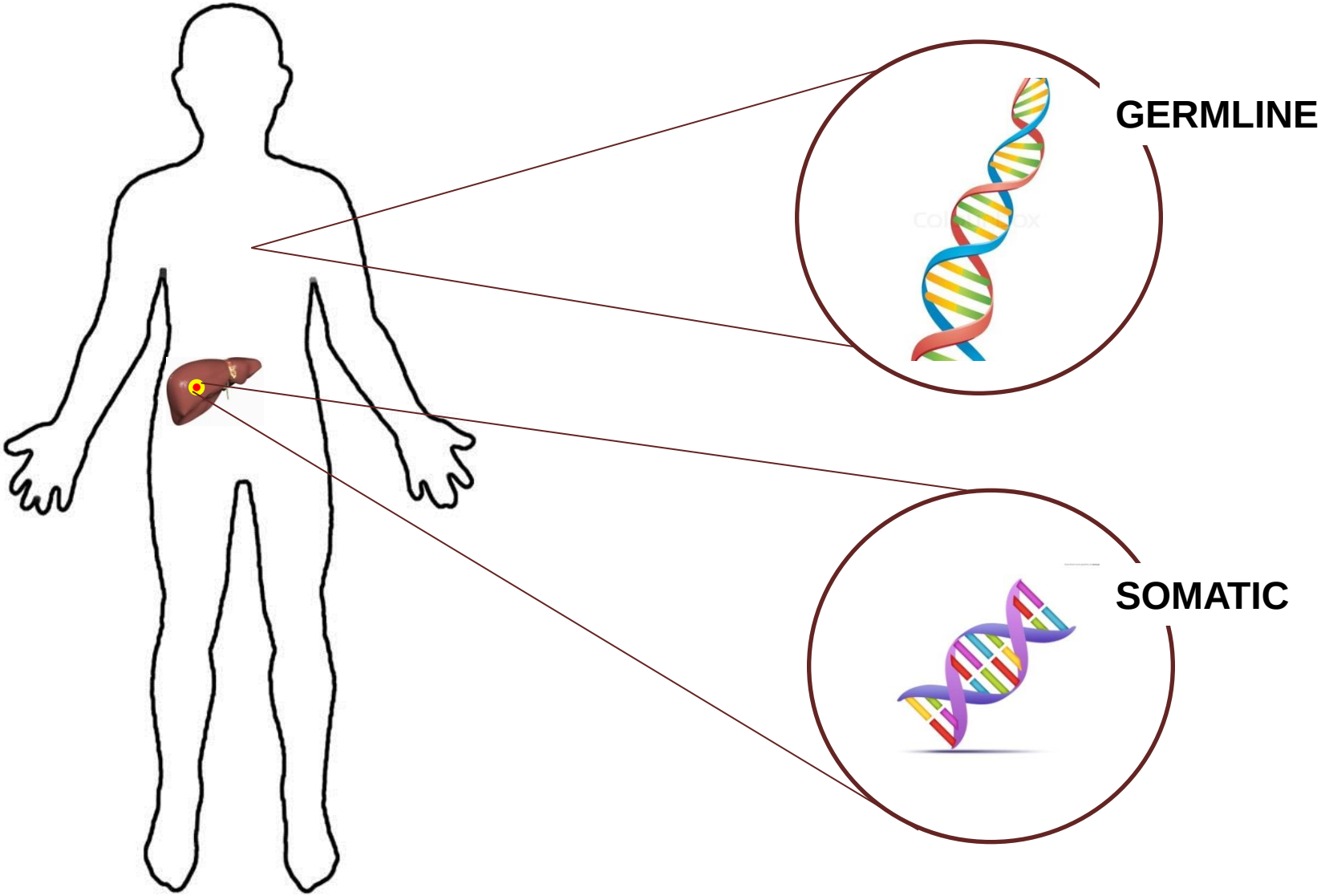
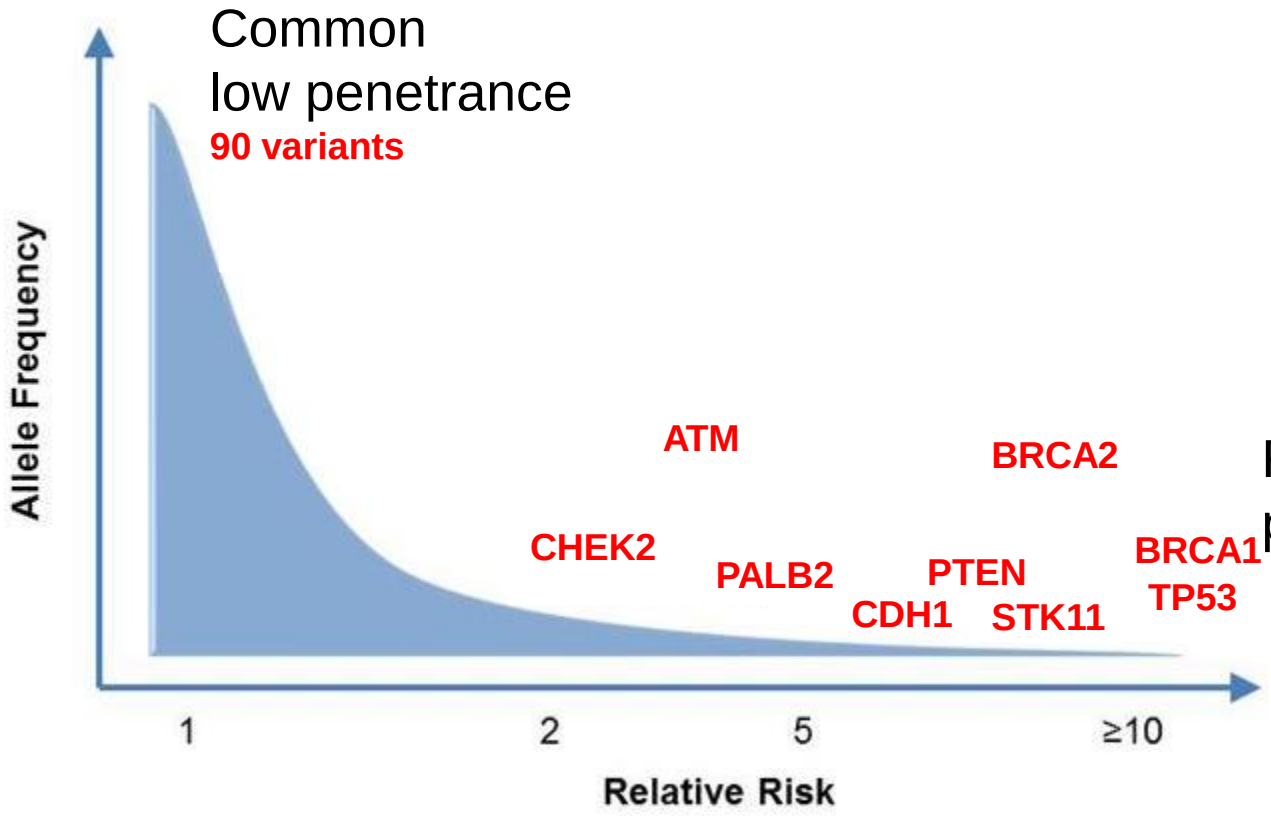
Cancer genomics is important in two contexts



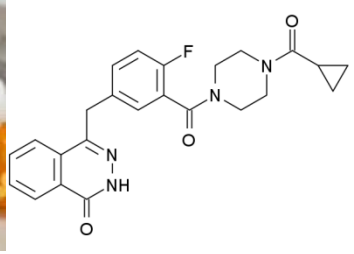
Breast cancer predisposition



Cancer predisposition genes have high clinical utility

Improved diagnosis

Optimised management and follow-up



Tailored therapies

Information for relatives
Cancer prevention

Cost efficiency

Rahman N. *Realising the promise of cancer predisposition genes.* Nature. 505:302-8 2014

Strong clinical and economic rationale for greater genetic testing of cancer predisposition genes

We need to test more genes in more people

Limitations of current clinical cancer genetics

1. Clinically and molecularly a low-throughput system.
2. Developed to limit access to testing.
3. Highly complex referral and testing eligibility criteria.
4. Primarily arose to meet needs of unaffecteds.
5. Not serving the needs of cancer patients well.

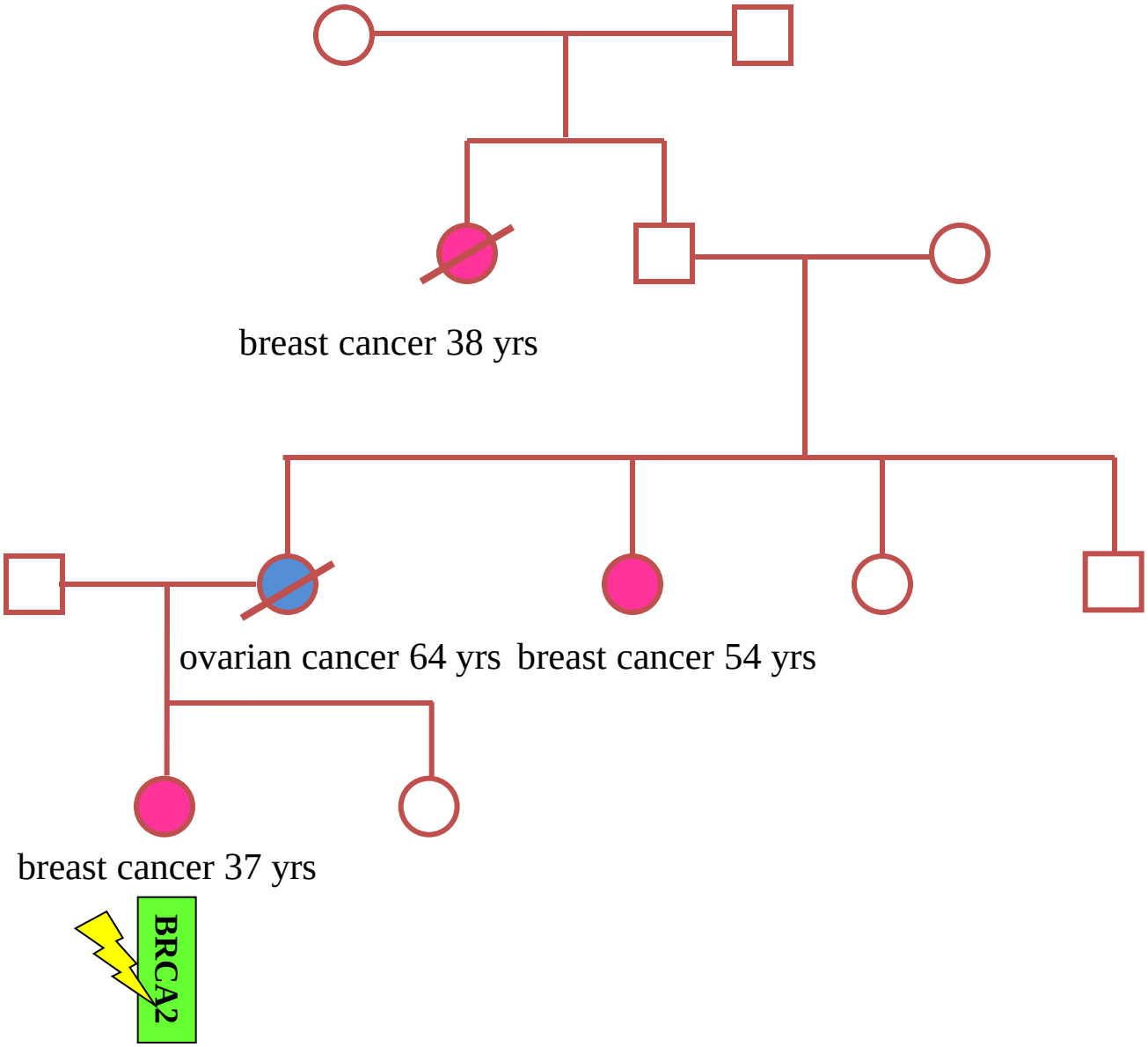
Medical genetics

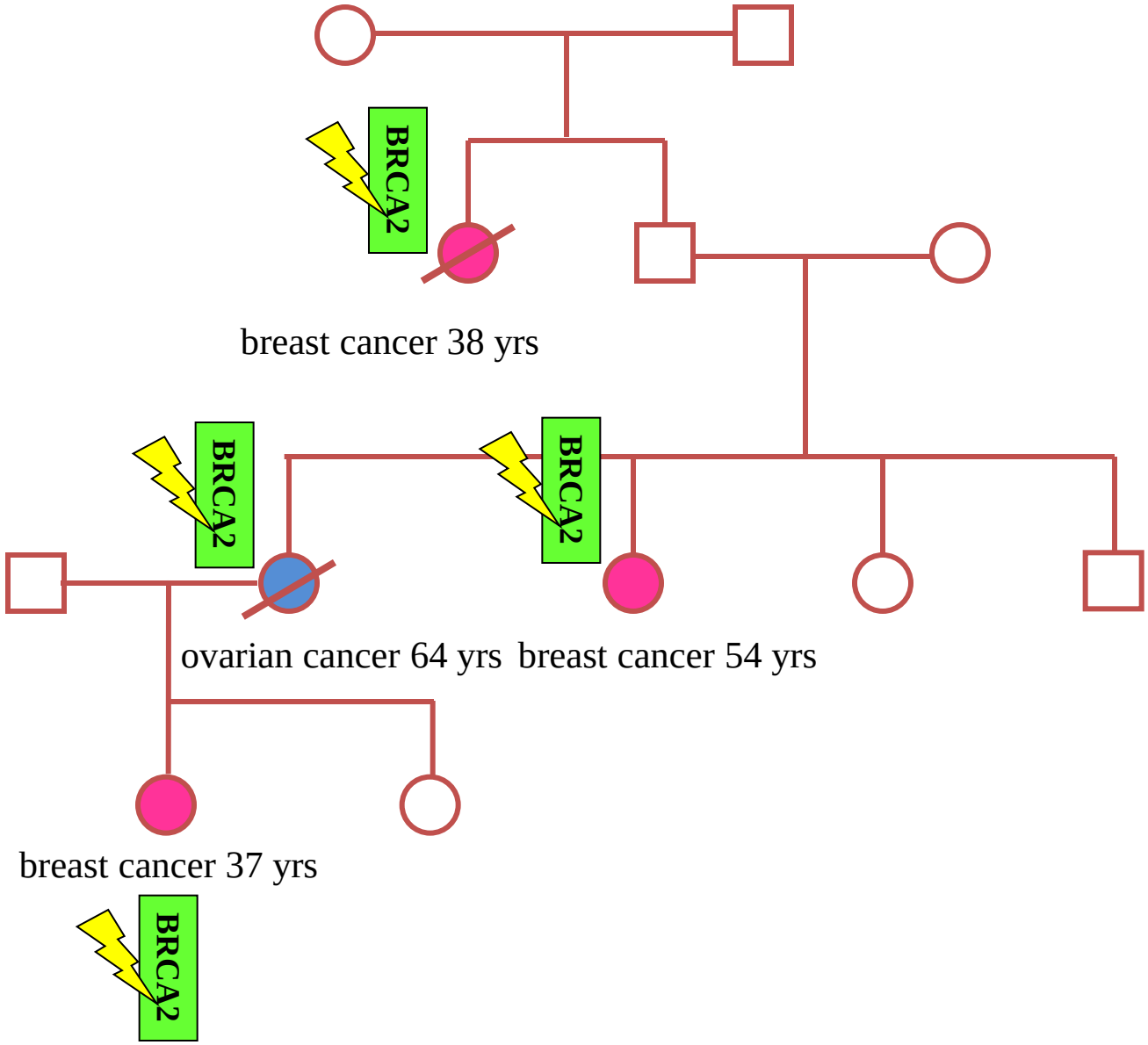
in people with cancer

vs

Predictive genetics

in healthy individuals


breast cancer 38 yrs
ovarian cancer 64 yrs
breast cancer 54 yrs
breast cancer 37 yrs
BRCA2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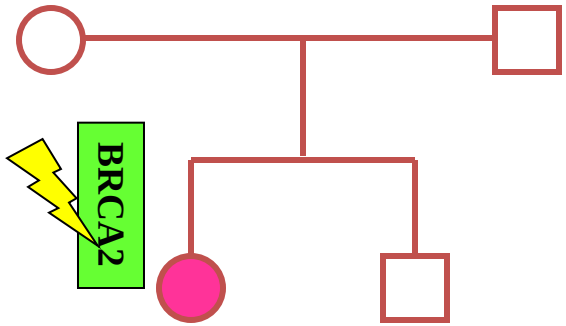

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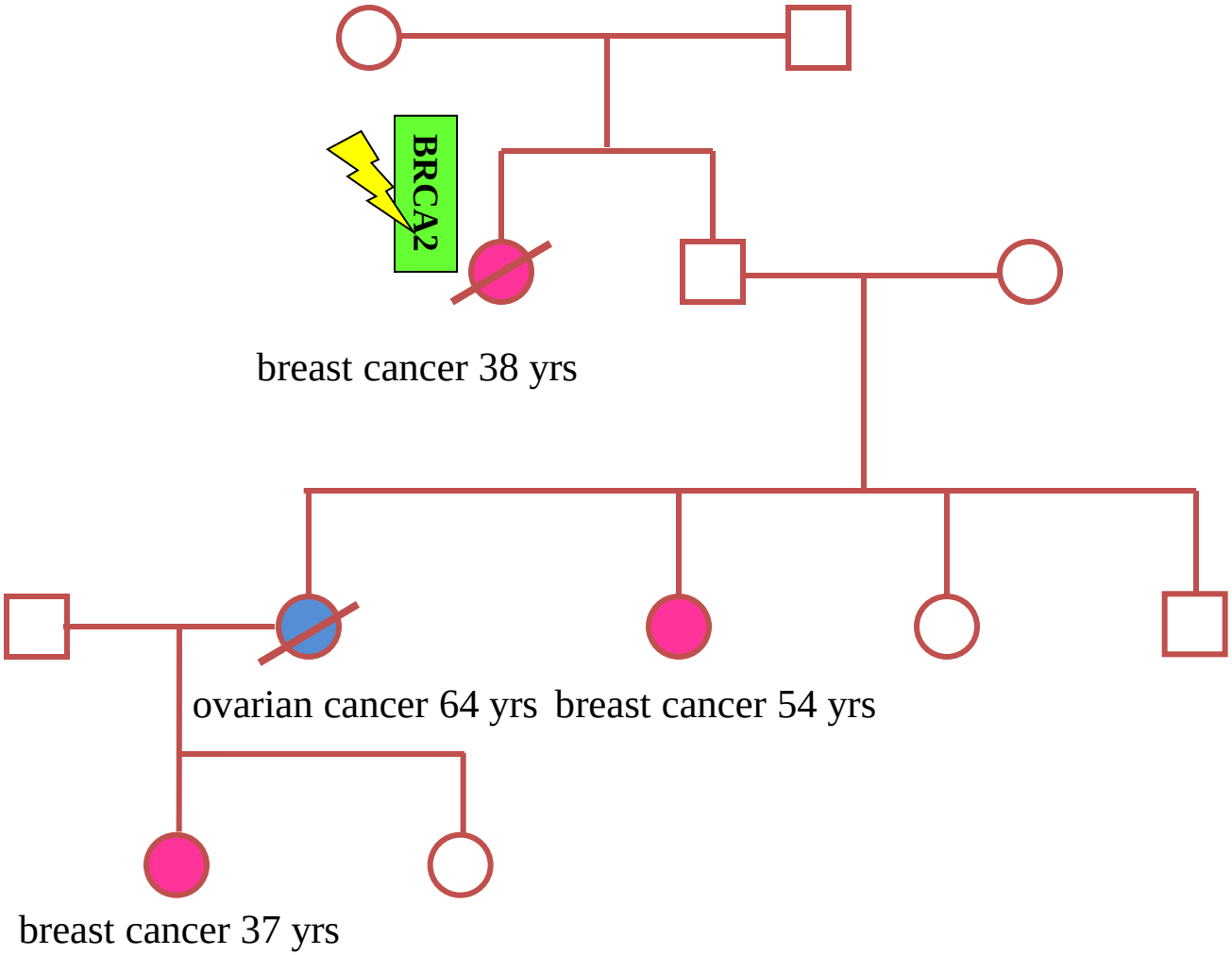
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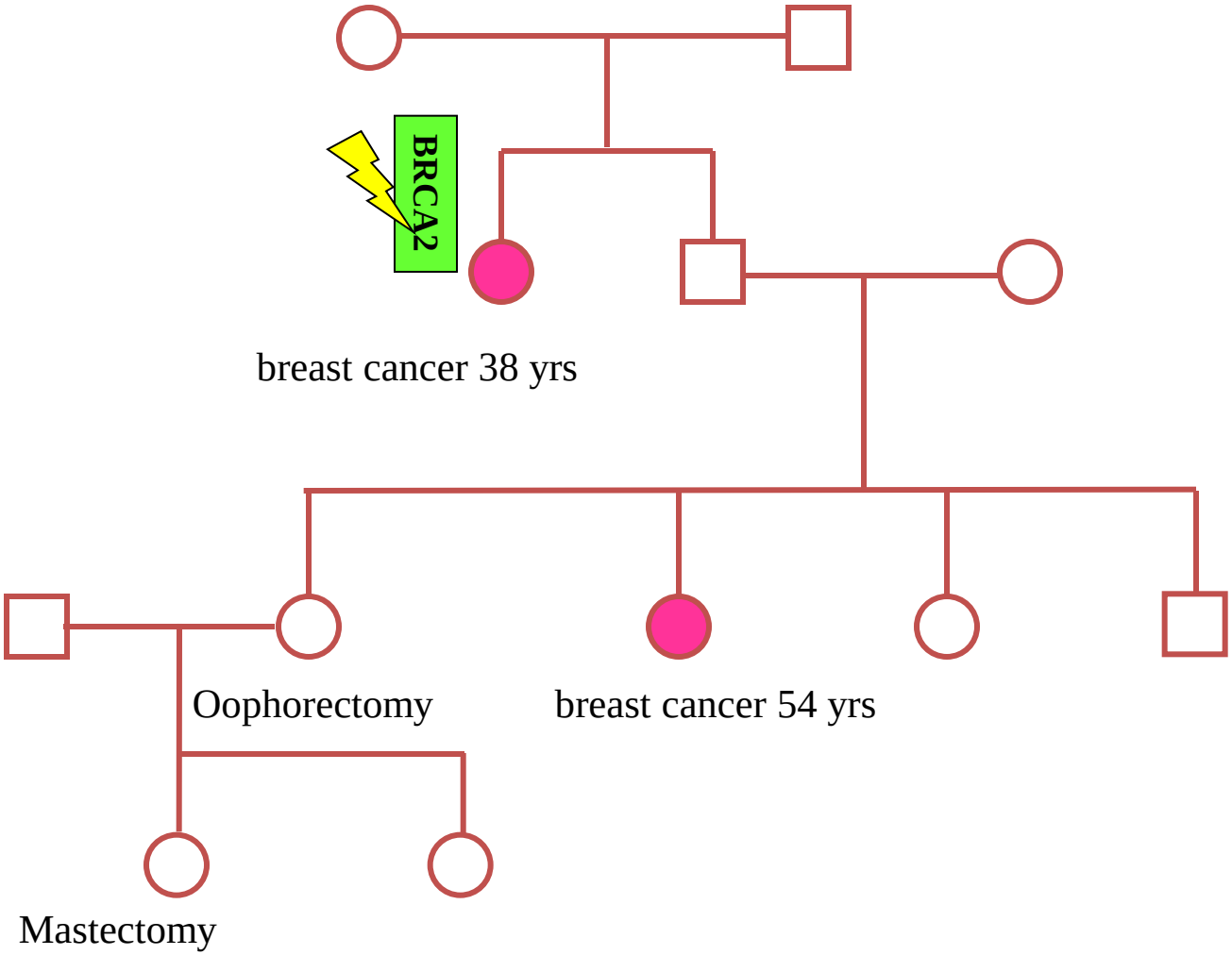

BRCA2
breast cancer 38 yrs
Oophorectomy
breast cancer 54 yrs
Mastectomy

Genetic testing in cancer patients is an effective and efficient way of preventing cancer

We need to offer testing to more breast cancer patients

??Genetic testing is easy??

Whole genome - $1000

??Genetic testing is easy??

Sequencing

Genetic Test

Sequencing

REBYHINEIHESTTOTE

Analysis

THE BOY IS IN THE TREE

Interpretation

HE MIGHT BE STUCK
- GET A LADDER

Genetic Test

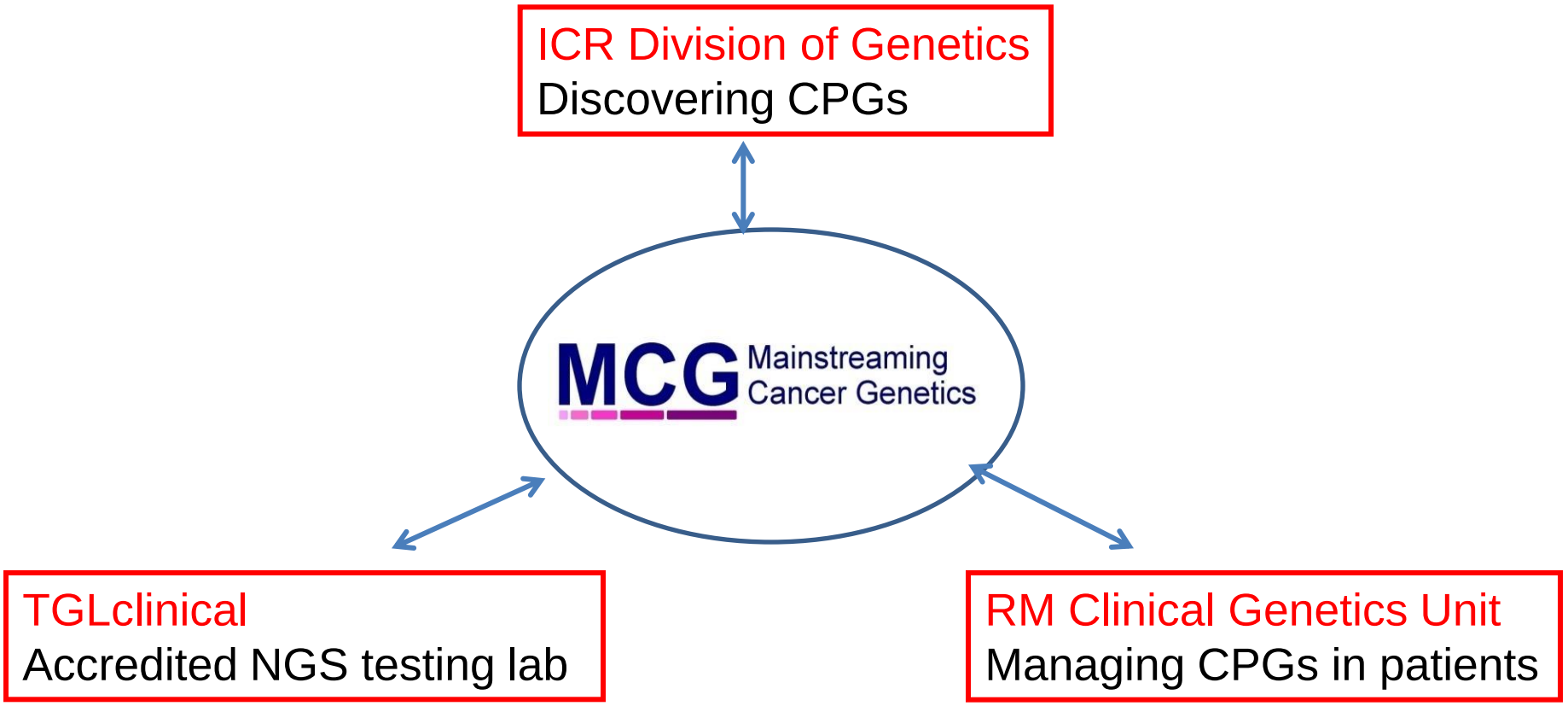
Patient Sample

Sequencing

Analysis

Interpretation

Clinical Report



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wellcome trust

Genetic Test

Patient Sample

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TruSight Cancer™

TruSight Cancer Panel (TSCP)

97	Genes/gene regions	1449 exons	1736 targets
260	Cancer GWAS SNPs		
24	Fingerprinting SNPs	287 SNPs	456 KB

0.01% of the genome

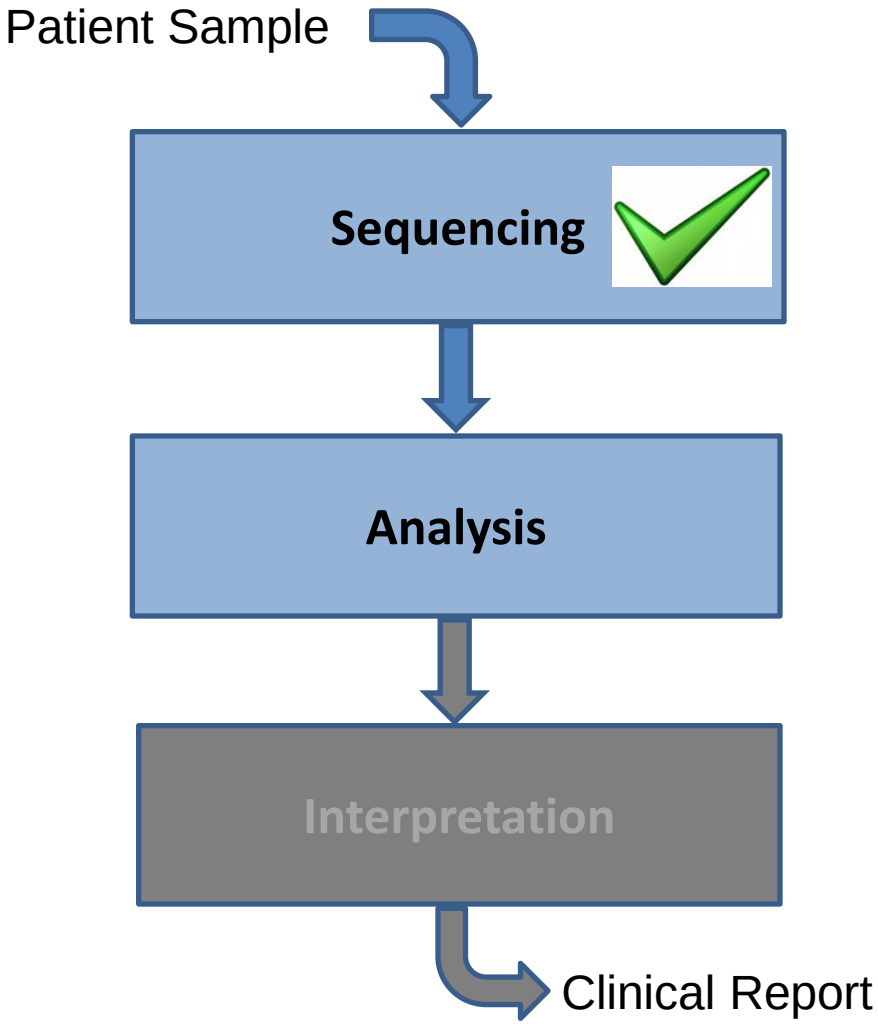
Simple + Robust
Low input (50ng)
Low failure rate
Easy lab process

High Capacity
576 samples / week / HiSeq2500
median 500X coverage

Majority of UK labs adopting TSCP

Shazia Mahamdallie
Anthony Renwick

Genetic test



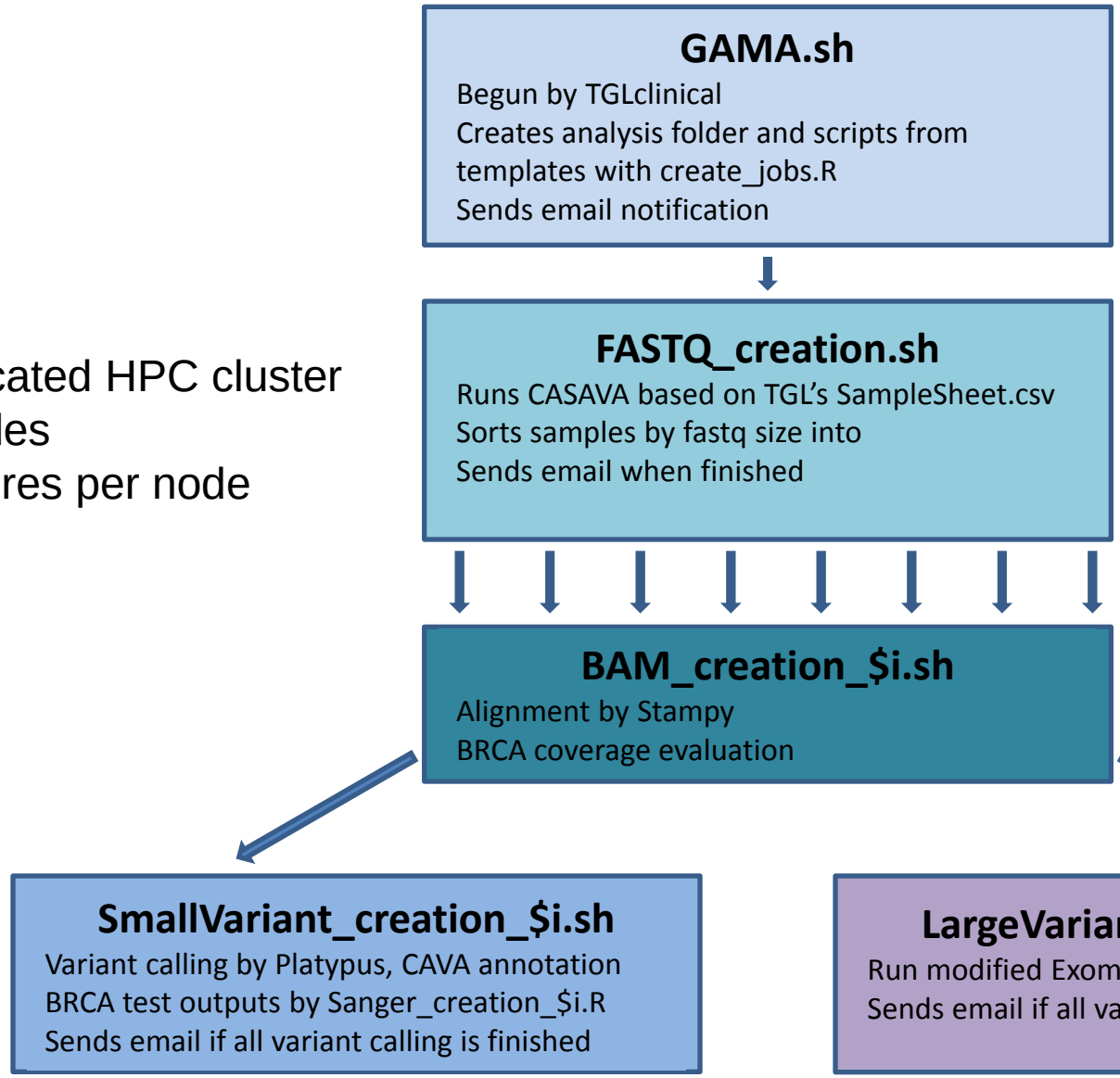
Analysis

Requirements for clinical genetic test analysis

- Fast
- Reliable
- Short hands on time

TSCP – custom analysis pipeline
< 1 min hands-on-time
No bioinformatician necessary
6-8 hours (overnight) for 96 samples

Tools available on http://www.well.ox.ac.uk/ogc/sequencing-tools



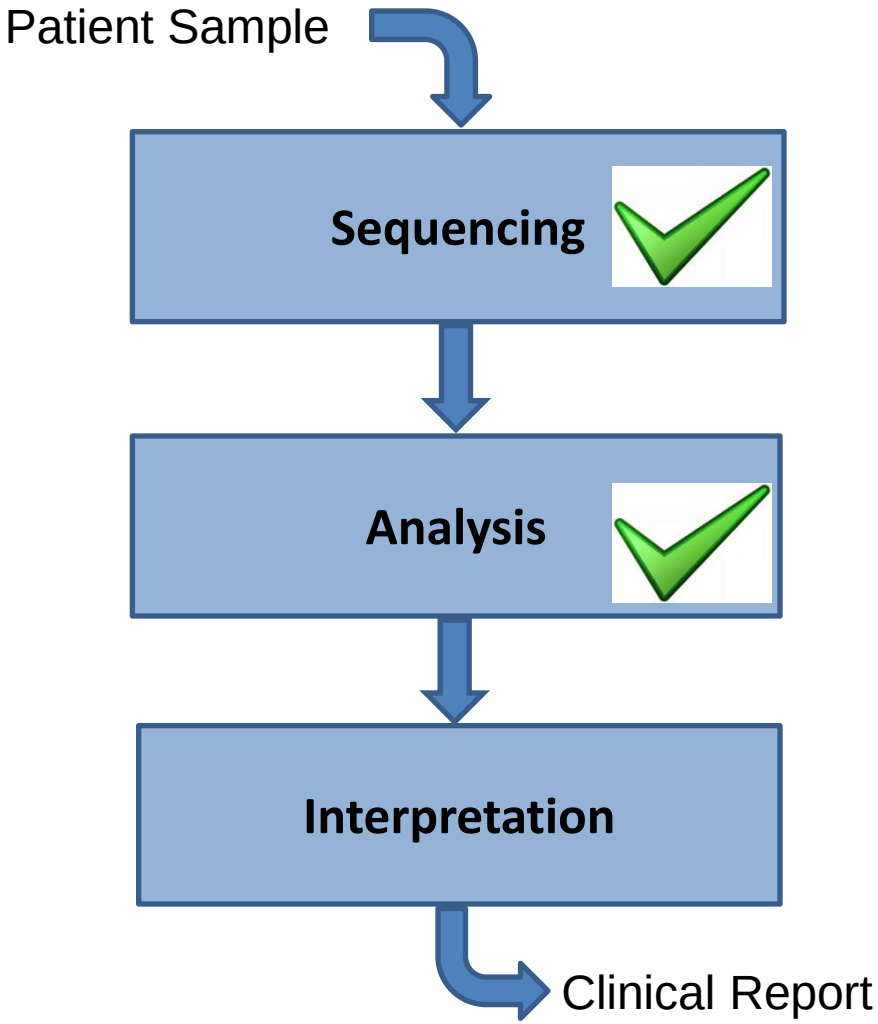
Dedicated HPC cluster
8 nodes
12 cores per node

96 samples – 8 hours
Small + large mutations
>99% sensitivity and specificity

Tools available on http://www.well.ox.ac.uk/ogc/sequencing-tools

Elise Ruark, Marton Munz
Anna Fowler, Gerton Lunter

Genetic test



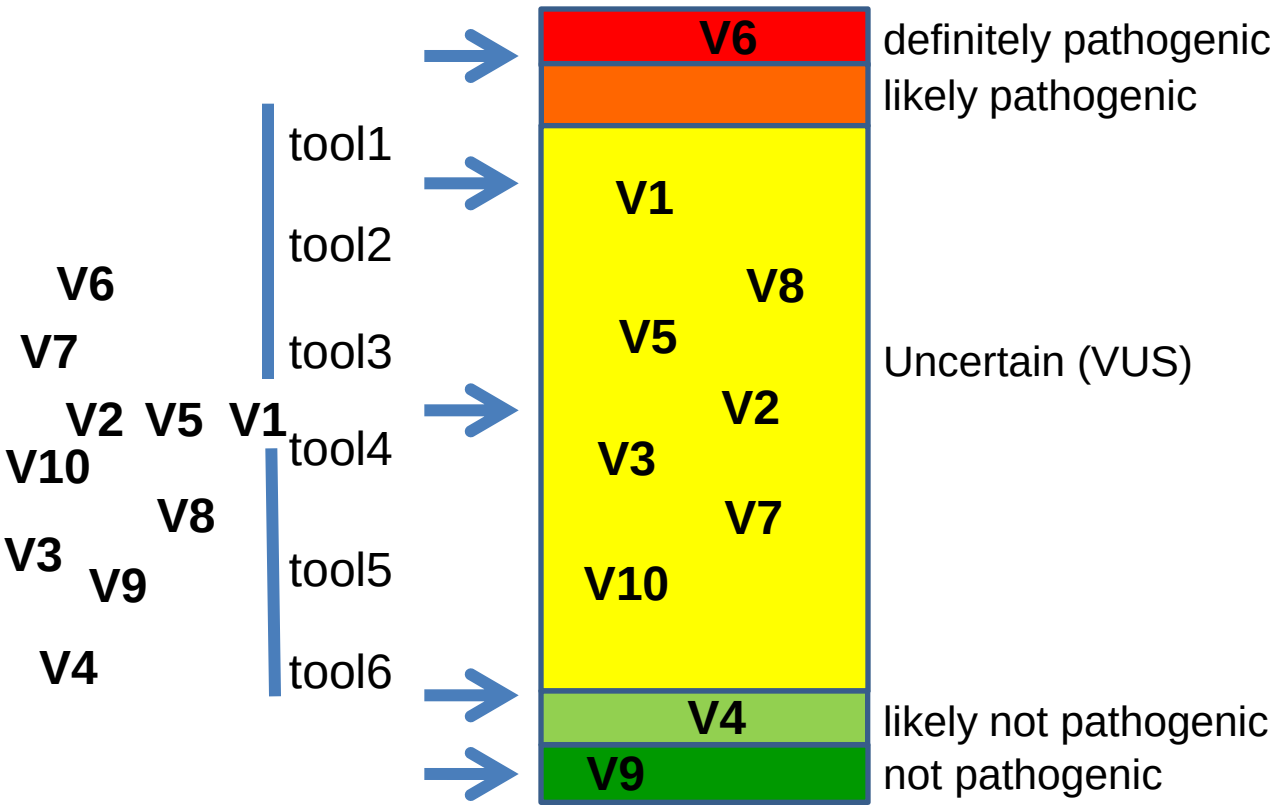
Traditional interpretation

1. Slow, laborious highly intensive analysis of each variant to decide if pathogenic.
2. Handled by specialised team.
3. Baseline: ‘guilty until proven innocent’.
4. Often final/interim classification was ‘uncertain’.
5. Often testing unaffected individuals - no immediate clinical management implications.

Interpretation requirements

1. Intelligible and usable by non-expert/patients
2. High-throughput + large volume
3. Fast turnaround
4. Avoidance of potential harms at individual and societal level

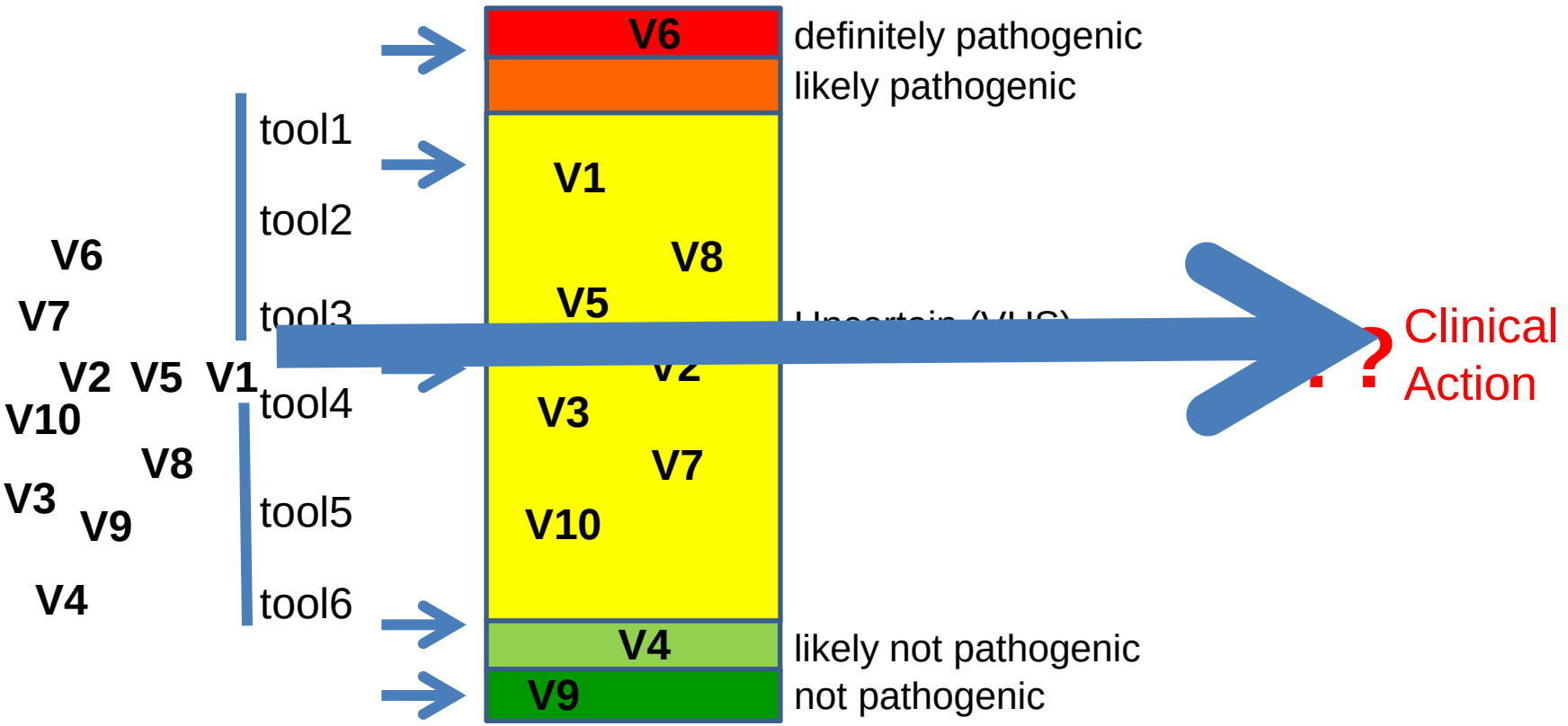
Academic variant classification



?? Clinical Action

Plon et al Hum Mutat 2008 29:1282-91

Academic variant classification



Plon et al Hum Mutat 2008 29:1282-91

BRCA genes are very variable in normal population

- 831 UK population tested with TruSight Cancer panel
- 4 pathogenic BRCA mutations (all truncating)

All BRCA variants

>5%	100%
up to 5%	44%
up to 1%	27%
up to 0.1%	13%

Missense BRCA variants

>5%	100%
up to 5%	37%
up to 1%	18%
up to 0.1%	9%

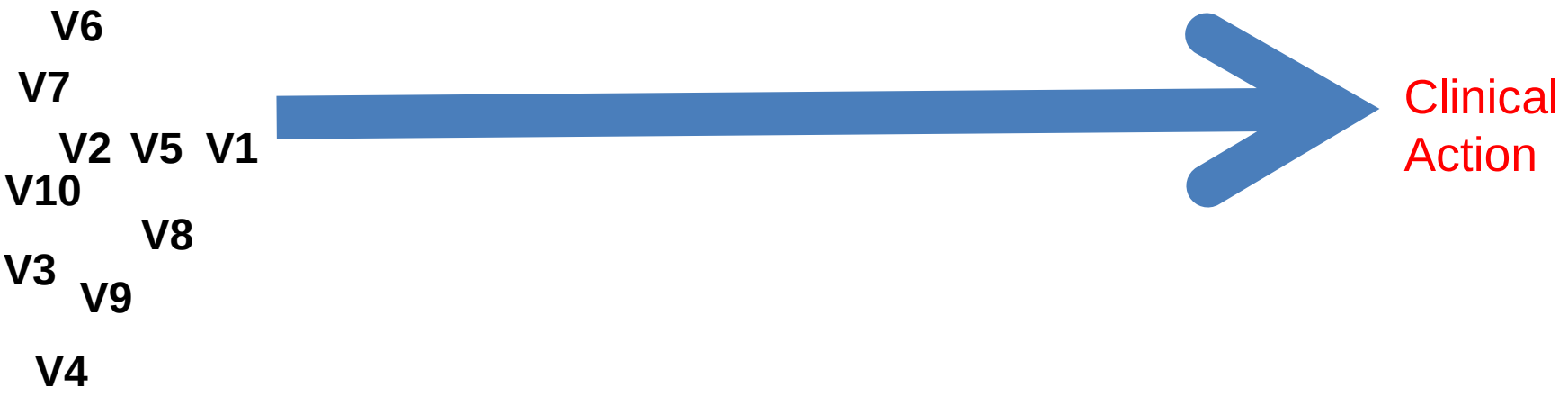
>95% non-truncating BRCA variants are not pathogenic

Potential harms of mismanagement of VUS

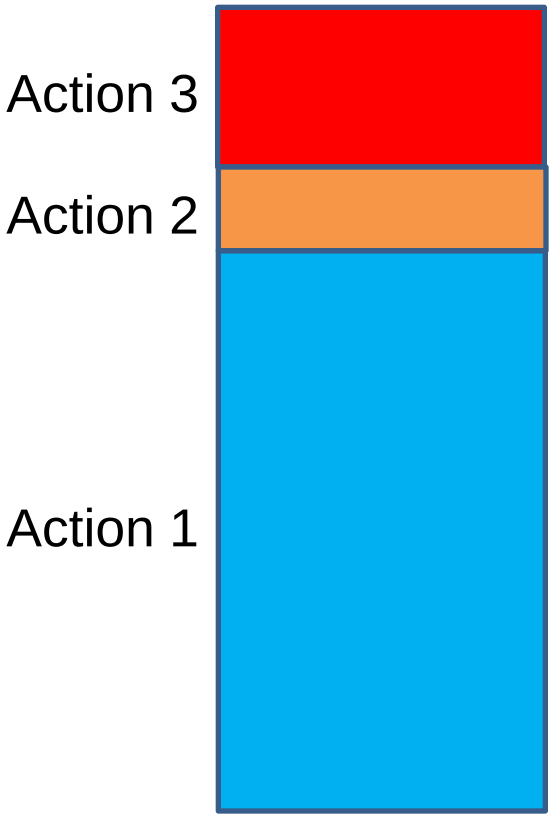
- Cancer surveillance for index and family
- Risk-reducing surgery
- Neonatal and prenatal testing / interventions

High potential for harm and financial burdens to health services

Clinical variant management

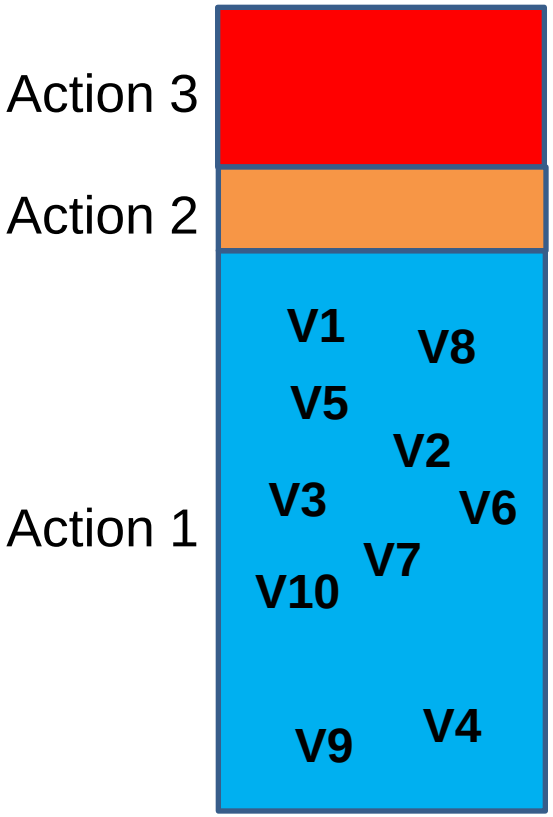


Clinical variant management



Manage as not clinically relevant

Clinical variant management



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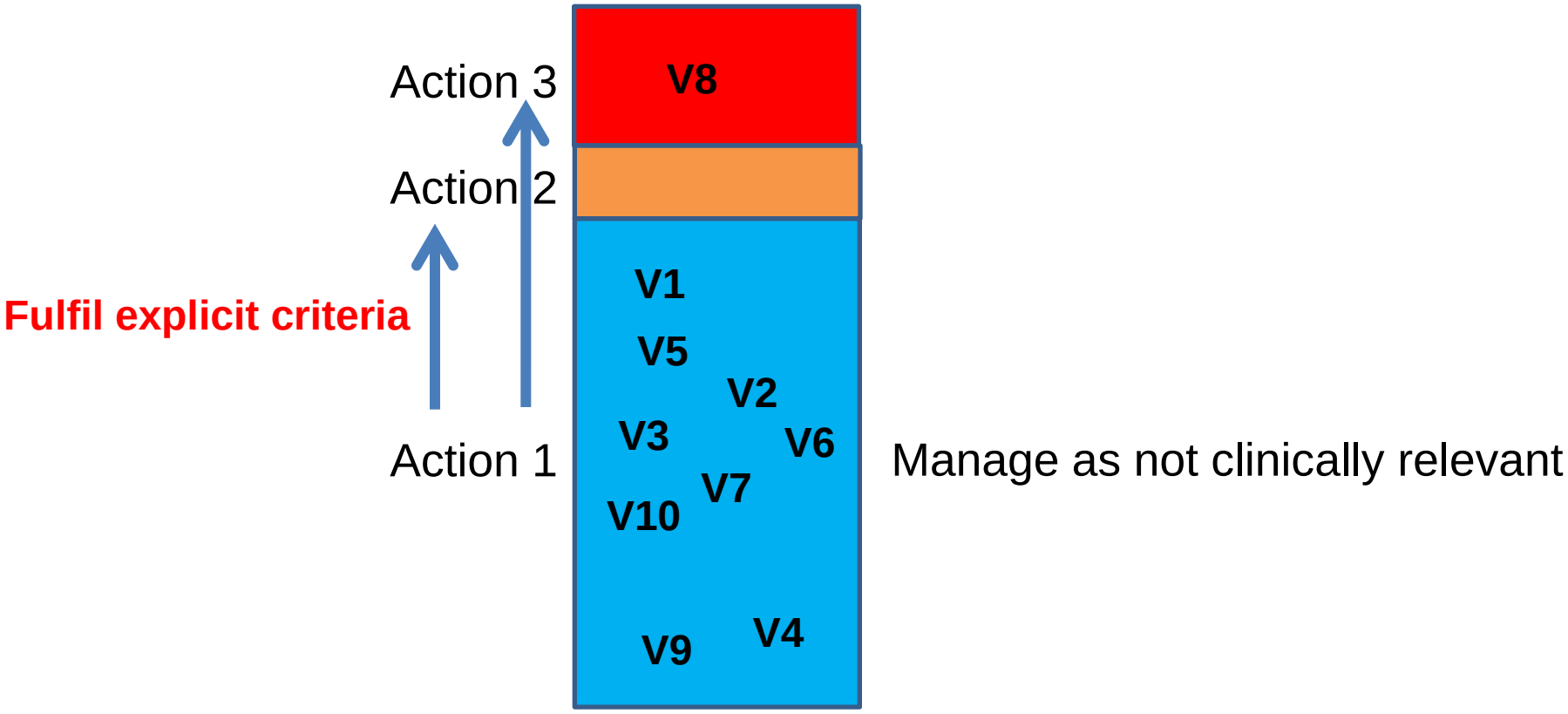
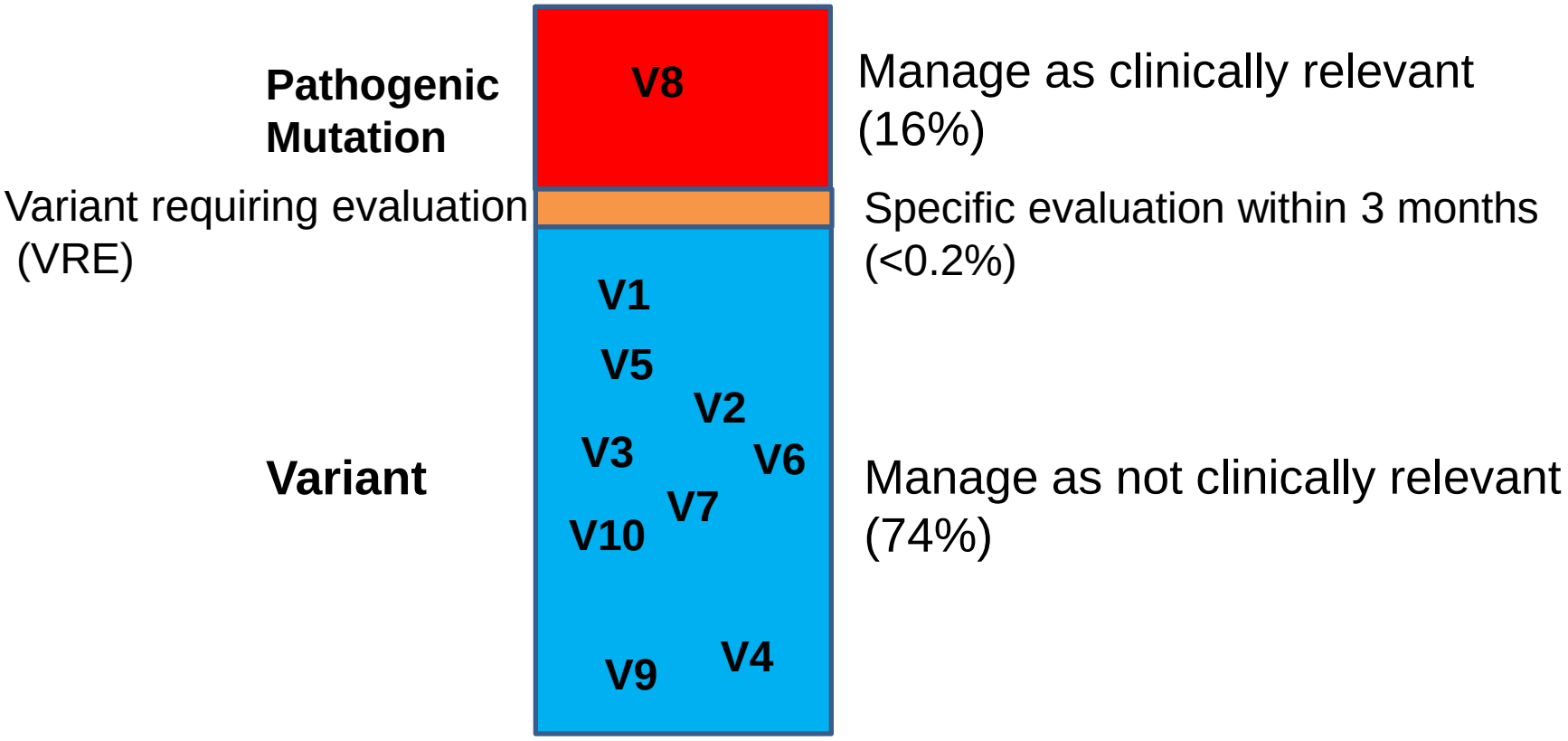
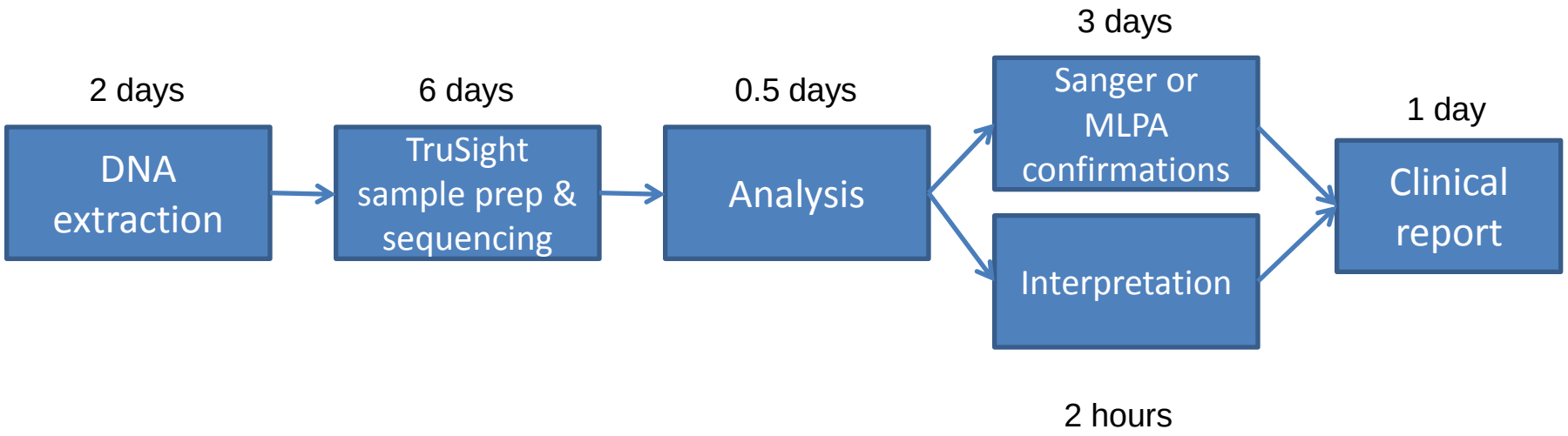


BRCA Clinical variant management



Gene test pipeline



Pipeline takes ~13 working days for 96-192 samples

Genetic Testing

Patient Sample

Sequencing

Analysis

Interpretation

Clinical Report

How can we implement large scale, routine testing?

Medical genetics

in people with disease

vs

Predictive genetics

in healthy individuals

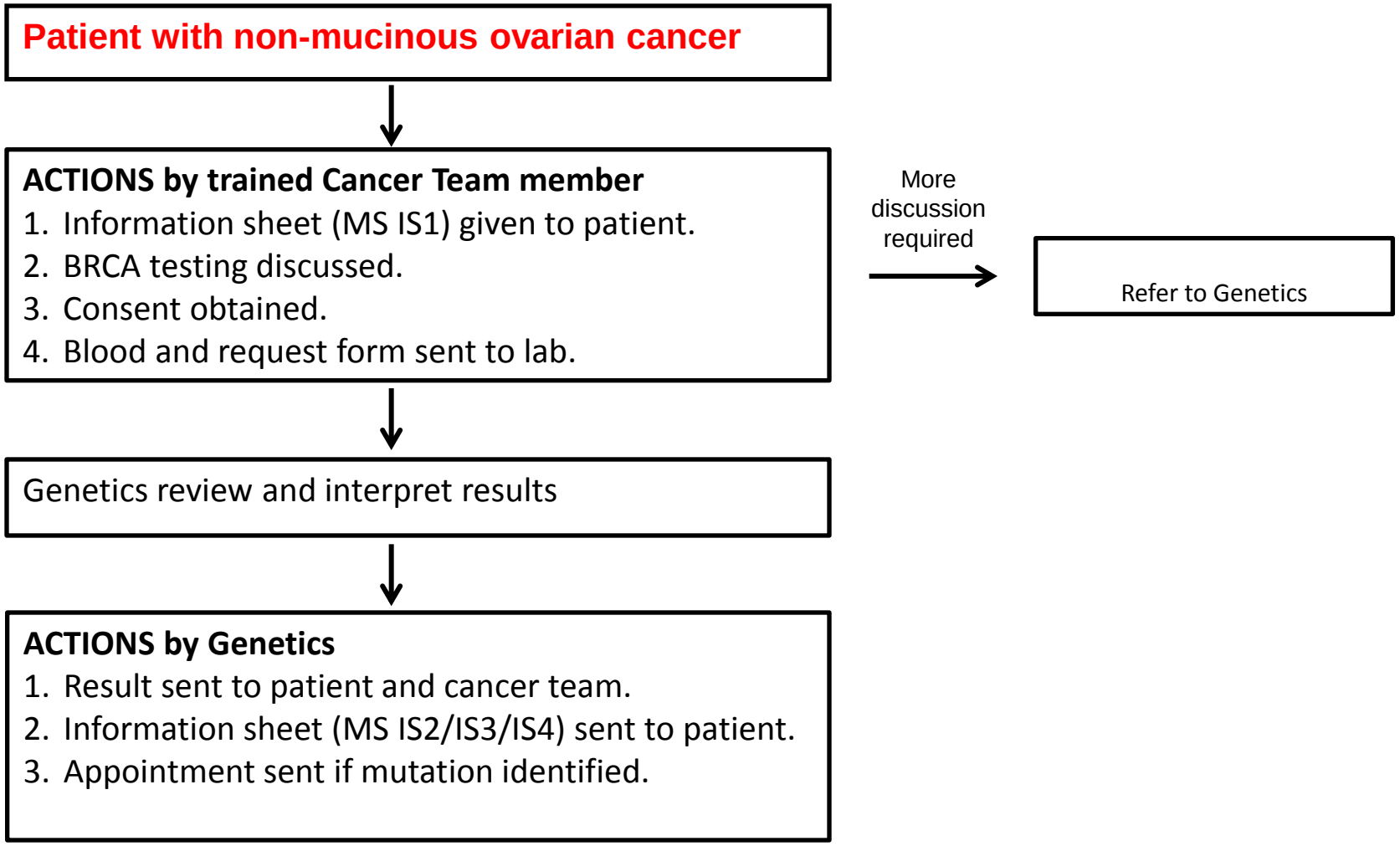
Mainstreaming 'Oncogenetic' Model

- Medical testing (i.e. in cancer patients) through 'trained' cancer team.
  - All test results interpreted by Genetics
  - Mutation – all sent Genetics appointment
  - No Mutation – likely no extra Genetics input needed.
- Testing in unaffecteds done through Genetics.

Started with BRCA testing in ovarian cancer

>15% ovarian cancer due to germline mutations.

- Major impact on cancer management
- Major opportunity for cancer prevention.
- Current eligibility complex and performs poorly.
- Inequity compared to breast cancer.
- Renewed interest because of PARP inhibitors.



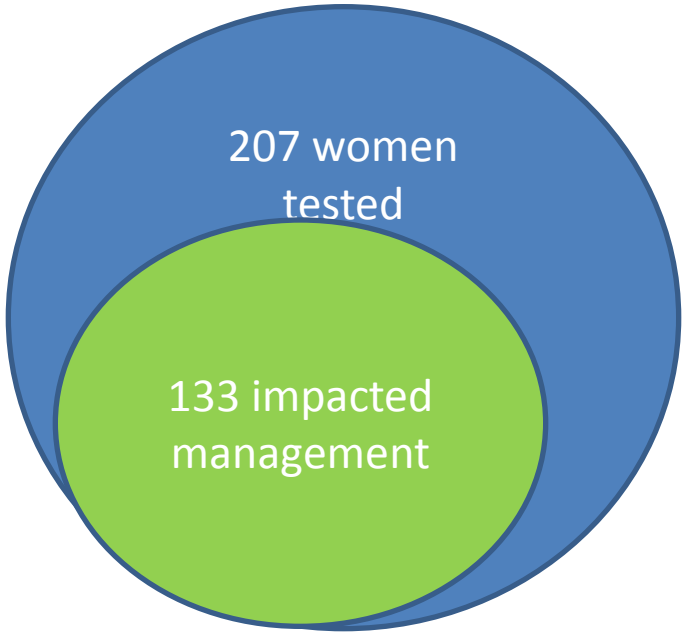
All resources available at www.mcgprogramme.com

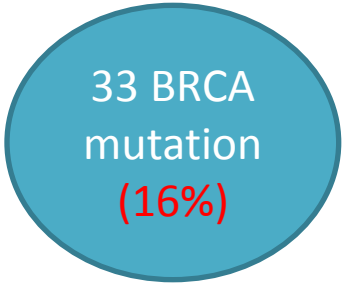
Simple training for non-geneticists

- Takes ~30 mins
- 4 short e-learning modules on YouTube
- Read documentation
- Complete checklist
- Receive certificate.

www.mcgprogramme.com/BRCAtesting

Ovarian cancer routine gene testing



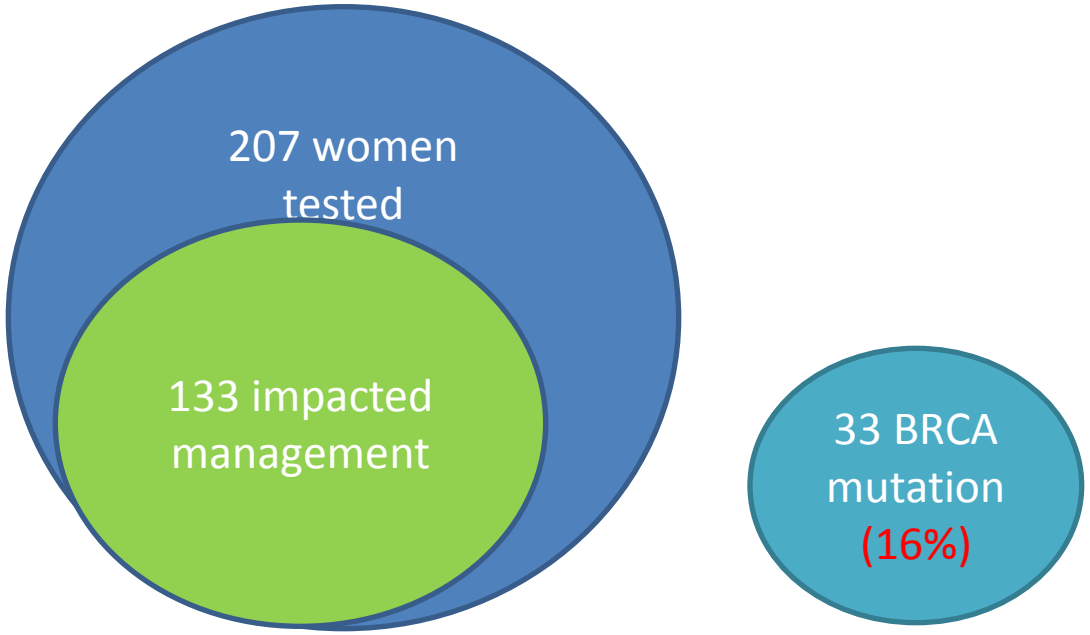


Only 10 met current testing criteria (but none had been referred)

<u>Patient impact</u>
Chemo treatment – PARP
Breast cancer risk management

<u>Family impact</u>
>80 relatives informed
39 have been tested

Ovarian cancer routine gene testing



EVERY patient offered test wanted it

Breast cancer BRCA mainstreaming

July 2013

- **Bilateral breast cancer, both <50yrs**
- **Triple negative breast cancer <50yrs**
- **Breast cancer + ovarian cancer - any age**

~10% threshold

54 patients
11 mutation positive
20% mutation rate

Feb 2015

- **Breast cancer <40 years**
- **Bilateral breast cancer - both <60 years**
- **Triple-negative breast cancer - any age**
- **Breast cancer + ovarian cancer - any age**
- **Male breast cancer - any age**

~5% threshold

Feedback

Patient feedback	Clinician feedback
• 100% pleased had test. • 100% happy to have test at oncology appt. • 98% understood may have implications for themselves and their families.	• 100%: I welcome the opportunity to carry out BRCA gene testing for cancer patients through oncology appointments. • 100%: I feel confident to consent a patient for a BRCA gene test; and inform patients of their results.

Effective and Efficient

Cost savings

4x throughput at ¼ cost

Time savings

<4 wks vs 21 wks

Many units are adopting all / parts of process in UK / Europe / USA

Genetic Testing

Patient Sample

Sequencing

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Clinical Report

Large-scale (96-192/wk)
Fast (3 weeks)
Affordable (£300)

Summary

Delivering large-scale, high-throughput genetic testing in breast cancer patients is achievable and can result in important clinical and economic benefits.

It requires integration of multiple disciplines and an appetite for change.

Acknowledgements

MCG Mainstreaming Cancer Genetics

ICR The Institute of Cancer Research

The Wellcome Trust Centre for Human Genetics

UNIVERSITY OF OXFORD

>200 people are involved in the MCG programme

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