

Assessing the genetic component of non-communicable chronic diseases

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GENOME RESEARCH INNOVATION

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Common Chronic NCD's

- PROBLEM = Majority of the disease burden



- SOLUTION = Personalized risk management
 - early detection of "**modifiable**" genetic contribution
 - AIM: Improve **Quality of Life** & reduce costs of care

THE CHALLENGE

Integrate genetics with other health disciplines in order to increase overall efficiency in diagnosis and clinical management



Examples from Africa

- HIV-Associated Nephropathy
- Breast carcinoma
- CVD / Metabolic syndrome / Diabetes mellitus
- Osteoarthrosis / Osteoporosis
- Vascular dementia / Alzheimer's disease

Key points

1. *Research*

- From single- to multi-gene disorders
- Genetic sub-typing of complex diseases

2. *Education*

- Educate the team
- Interdisciplinary approach

3. *Service*

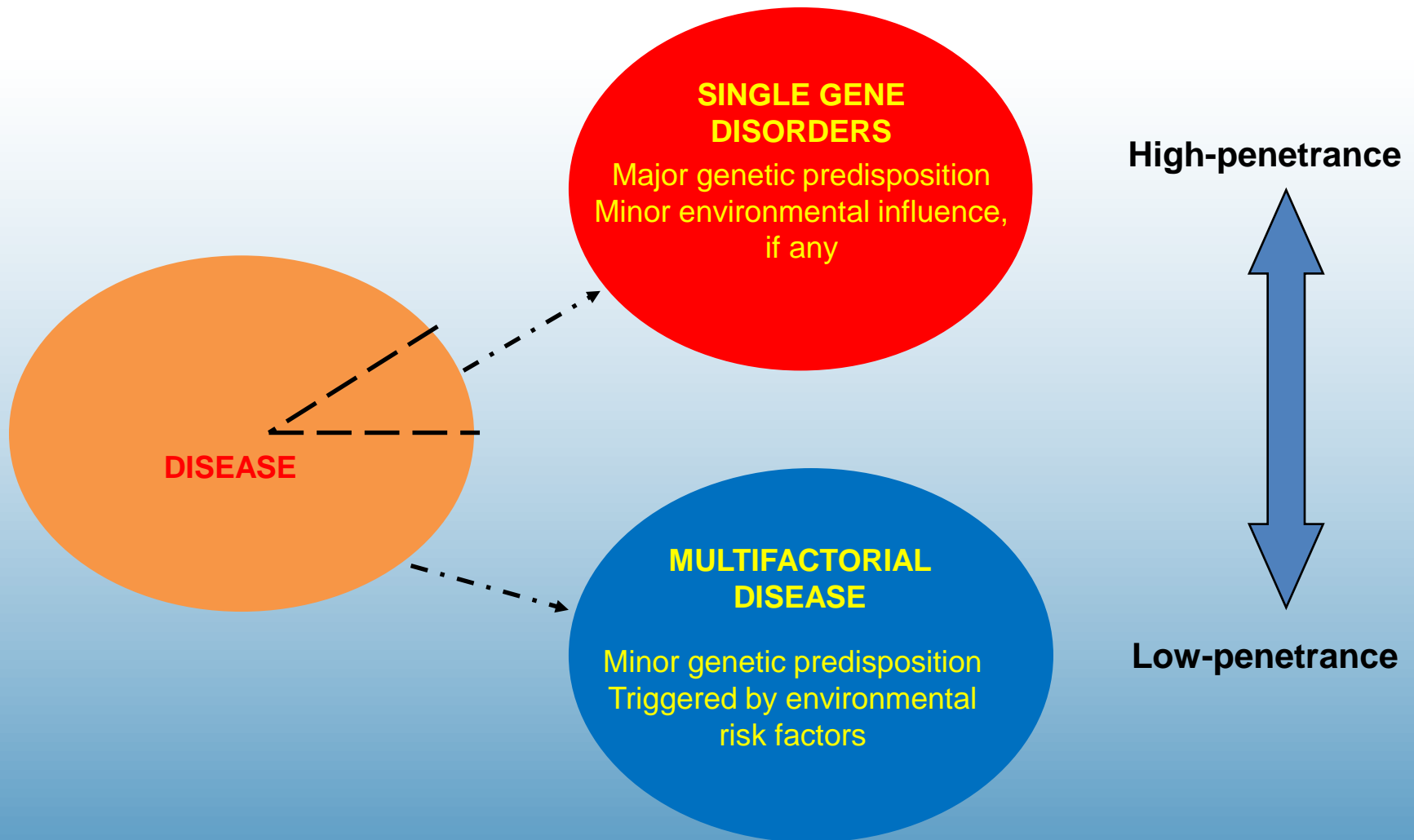
- Shared platform for research and service delivery

FUTURE FOCUS: Clinical sequencing (exome/whole genomes)

Research

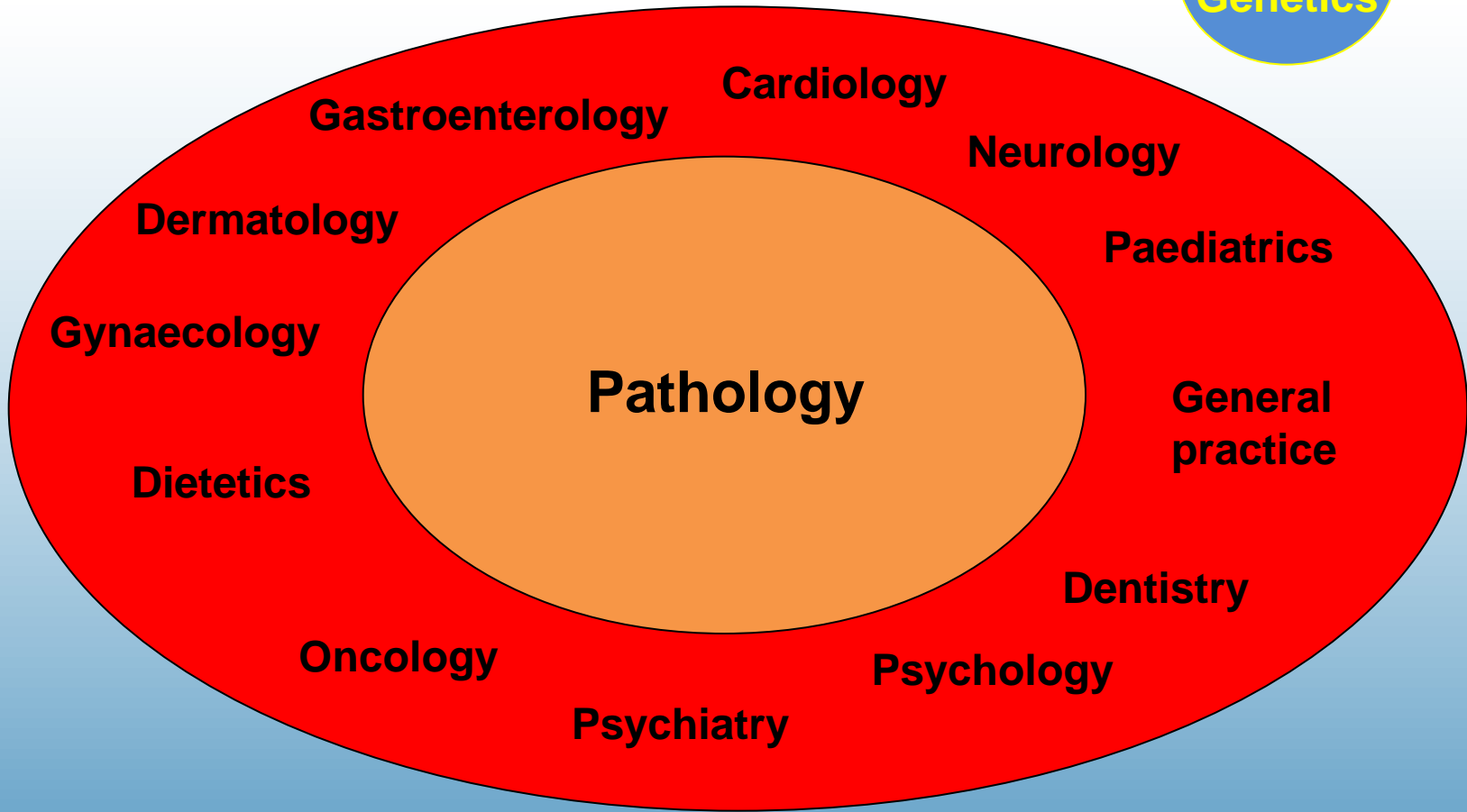
Establishing the Scientific Foundation

From single- to multi-gene disorders

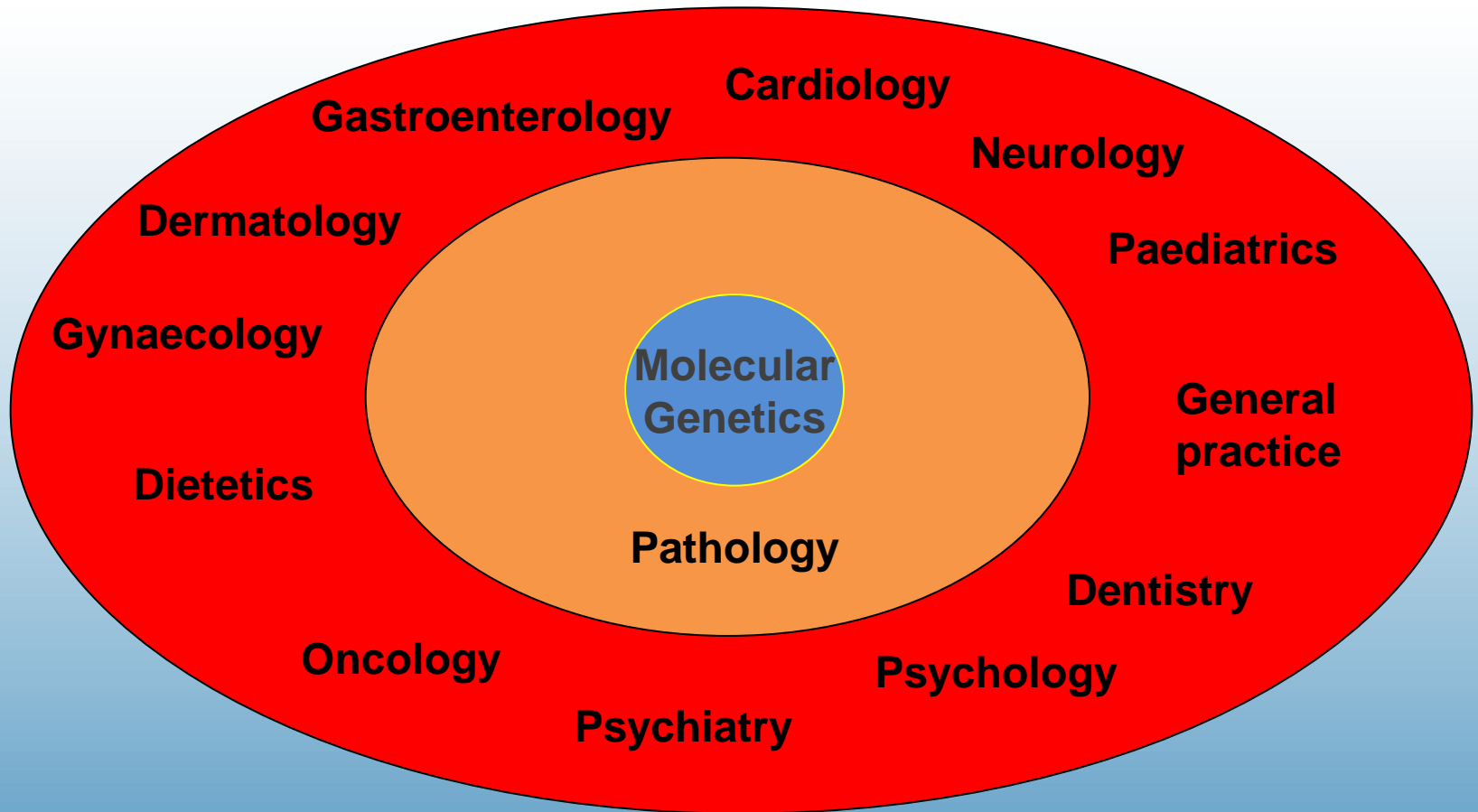


Stand-alone laboratory science

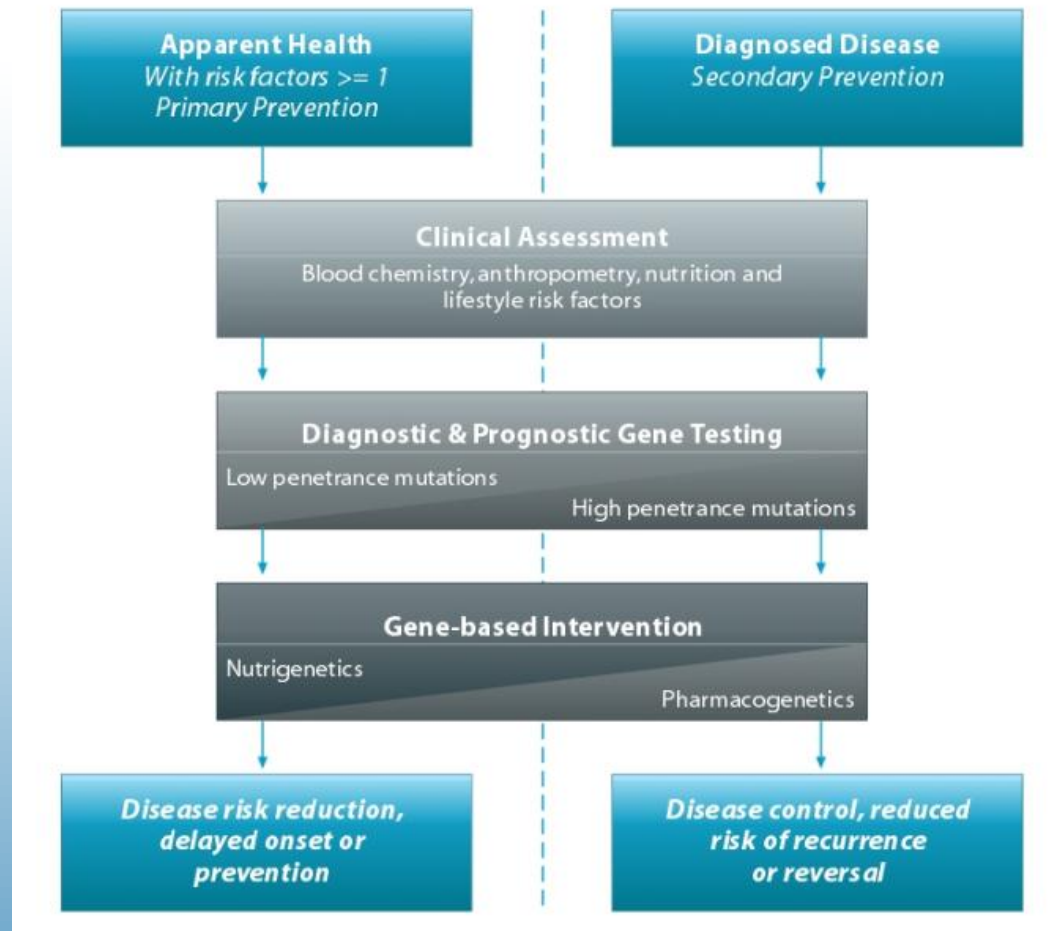
Molecular Genetics



Genetic Knowledge Integration



Pathology supported genetic testing



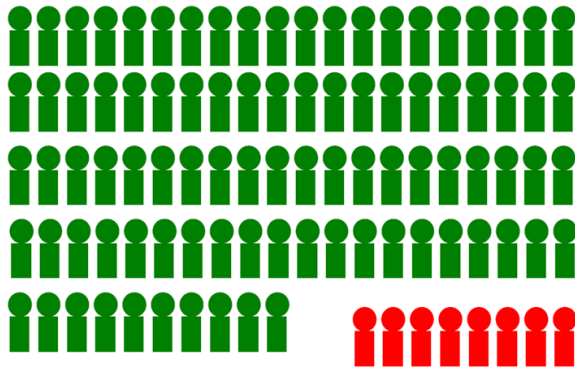
Population-based health recommendations apply in mutation-negative individuals, based on the clinical risk profile

Anatomical Pathology Application

The Problem For Using Chemotherapy

(Most Common Presentation Of Breast Cancer Today: T1 N0 ER+ Grade 2 Postmenopausal)

Need To Treat 100 Women



And Only One Benefits !

From: Dr Rika Pienaar

**Only FDA Approved Multi-gene Breast Cancer Specific Prognostic Test:
February 6, 2007**

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THIS WEEK IN THE JOURNAL

Article Summaries 1993
 Perspective: Predictive Molecular Pathology 1995
 Perspective: Herbal Medicines — What's in the Bottle? 1997
ORIGINAL ARTICLES
 A Gene-Expression Signature as a Predictor of Survival in Breast Cancer 1999
 Effect of Dialysis Dose and Membrane Flux in Maintenance Hemodialysis 2010
 Comparison of Caspofungin and Amphotericin B for Invasive Candidiasis 2020

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL
 A 35-Year-Old Man with Headache, Deviation of the Tongue, and Unusual Radiographic Abnormalities 2007

EDITORIALS
 Molecular Signatures of Breast Cancer — Predicting the Future 2007
 Success and Challenge in Dialysis Therapy 2008
 Echinoscinidin — An Advance in the Primary Treatment of Invasive Candidiasis 2070

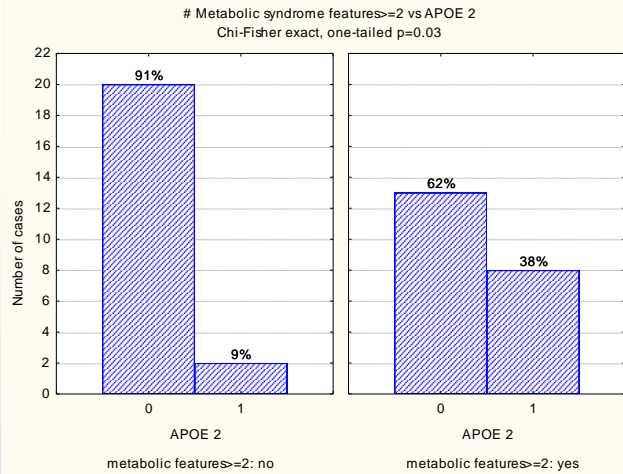
SOUNDING BOARD
 Botanical Medicines — The Need 173

JMA
 Myosin A

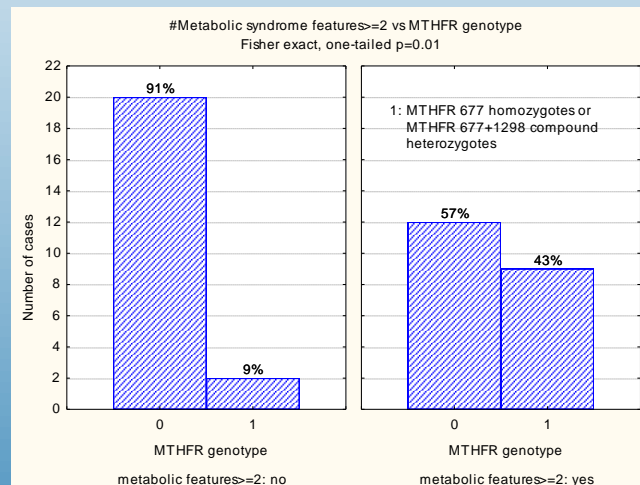
Stratification

Approach	Survive	Die	Good Prognosis	Poor Prognosis	Poor Prognosis
Unstratified breast cancer	70%	30%	-	-	-
St. Gallen	15%	85%	15%	85%	-
MammaPrint	40%	60%	40%	60%	50%

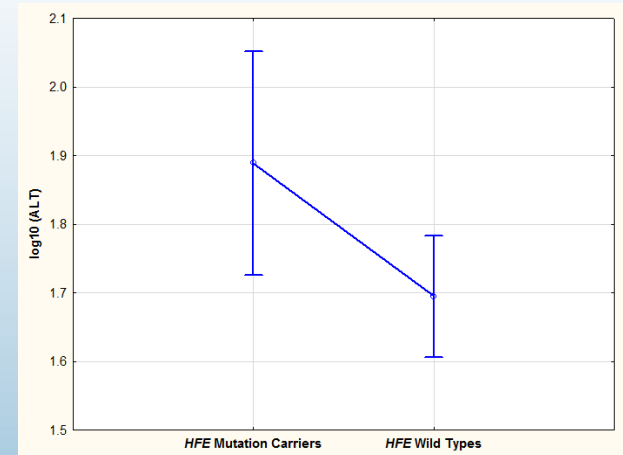
Chemical Pathology Application



Dyslipidaemia



Non-alcoholic fatty liver disease



From: Dr Corne Kruger & Leslie Fisher

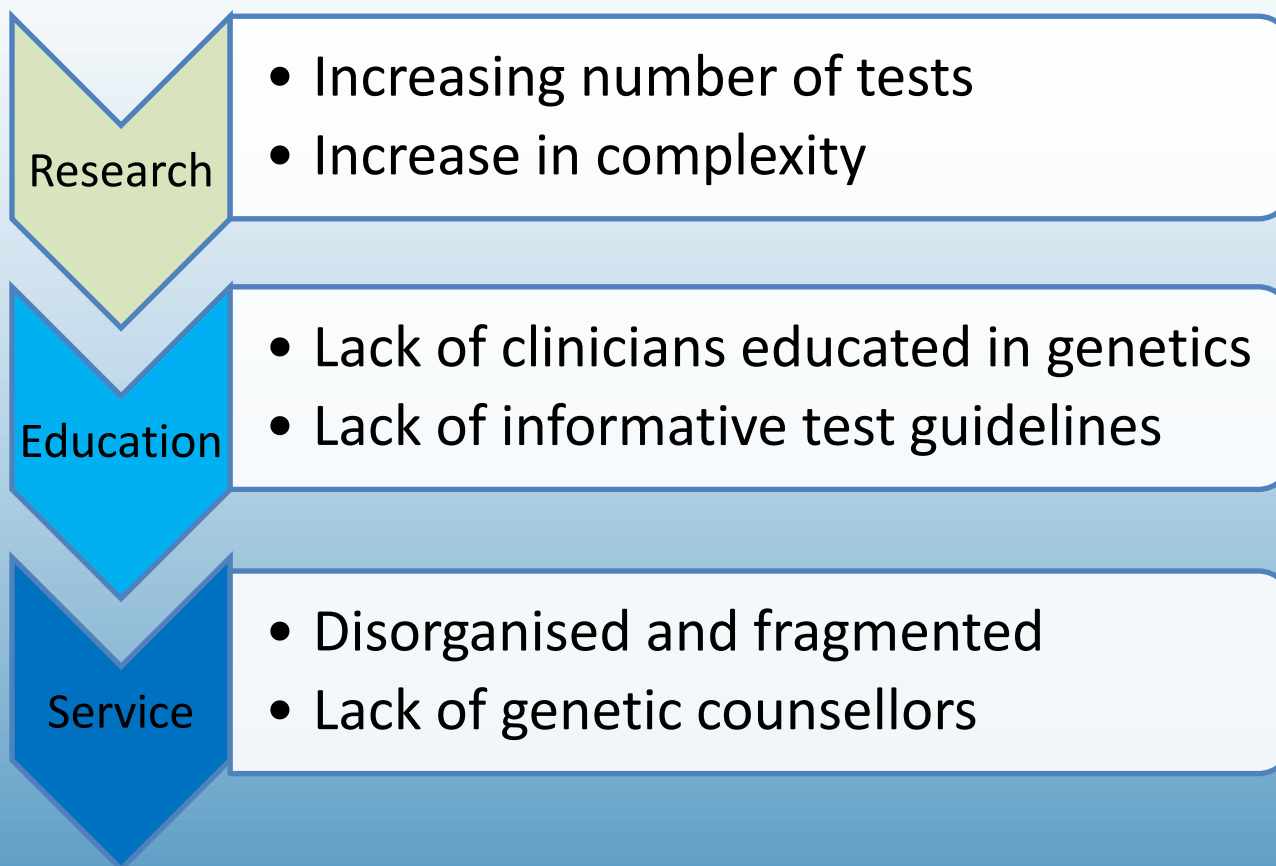
**Methylation pathway:
CVD and cancer risk**

Education

Establishing the Clinical Interface

Problem statement

Transfer of genetic knowledge into clinical practice



Bridging the professional gap

CLINICIANS

- *Indication:* which genetic tests contribute to better healthcare?
- *Application:* how to apply test information in Dx & Rx?
 - Educational needs: what are the limitations of genetic testing?



SCIENTISTS

- *Context:* where do genetic tests add value?
- *Clinical Information:* what information has clinical relevance? (marketing)
 - Ongoing R & D: Continuing capacity to produce scientific knowledge

Needs analysis to guide the way forward

- Questionnaire-based survey
 - Educational tool
 - Resulted in a significant shift from past to future intended use of genetic testing
 - Comprehensive genetic testing preferred
 - Computer-based CDSS preferred
- Applied genetics
 - Integrative Medicine Course

Service

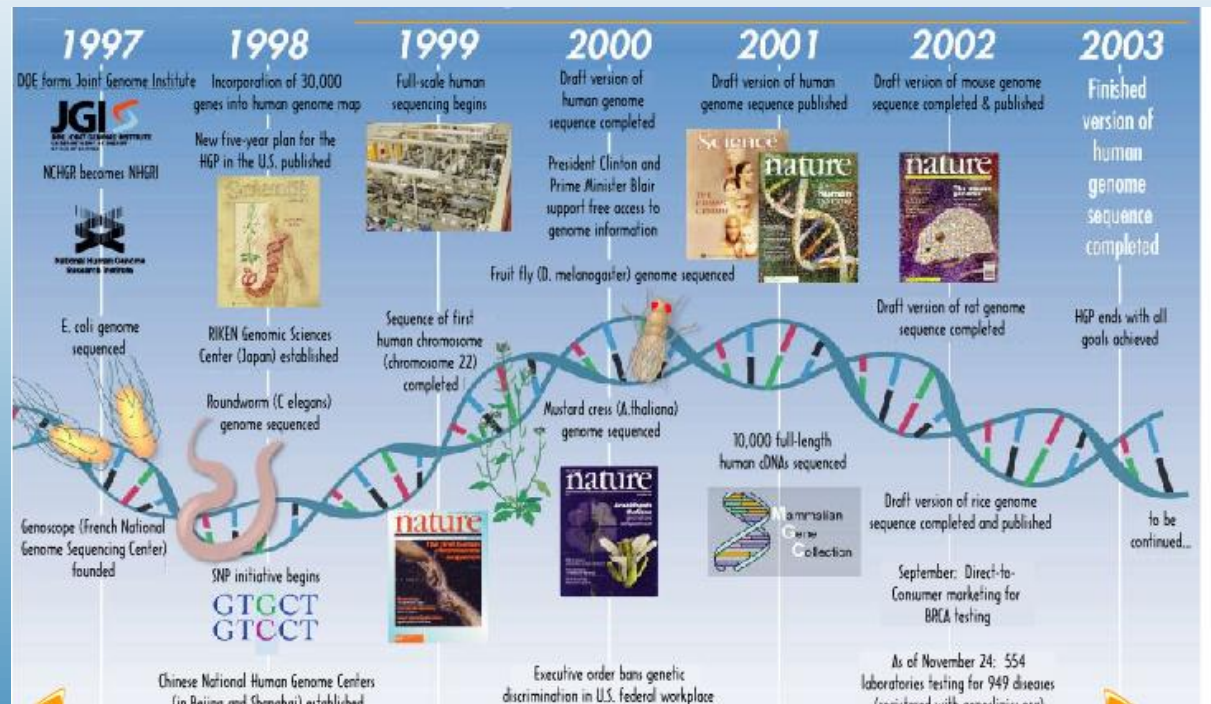
Clinical geneticists and genetic counsellors

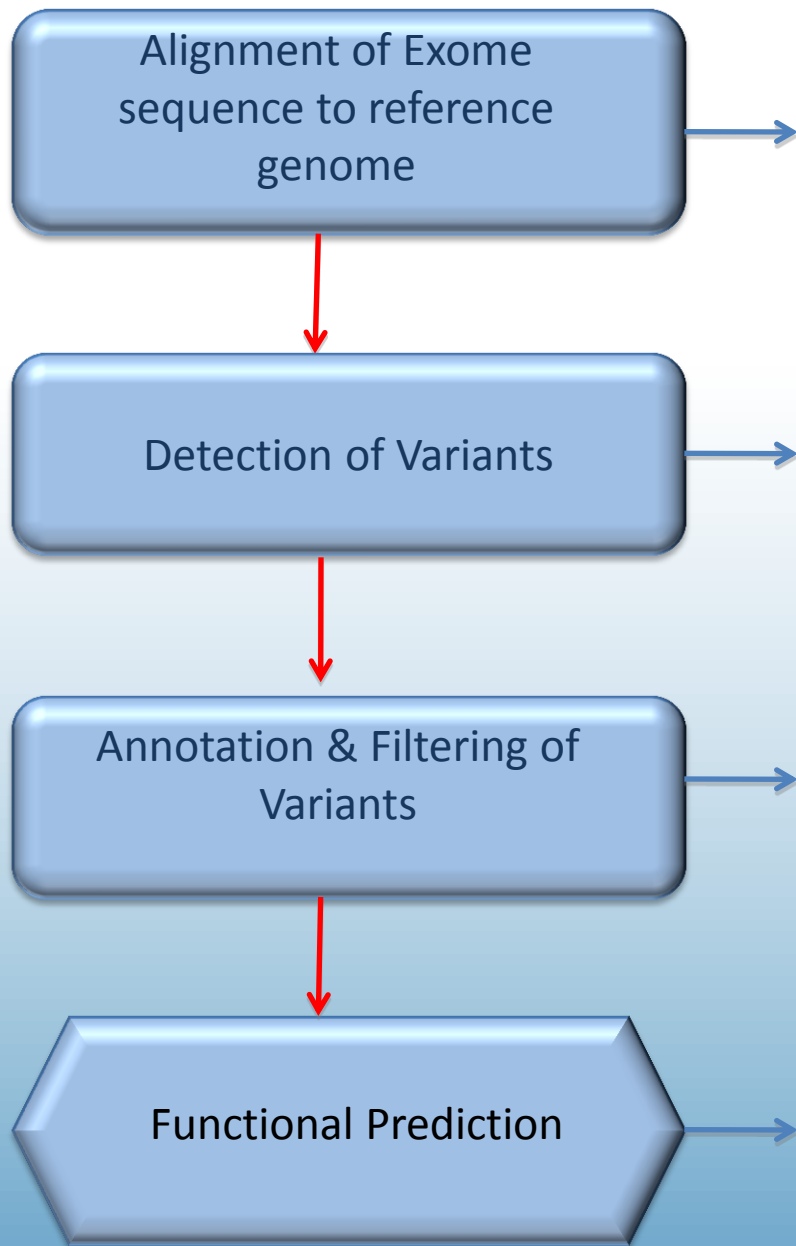


Ultimate **Patient Benefit**

Future focus: Exome/genome sequencing

Match disease diagnosis and therapeutic design with the genetic profile of the patient



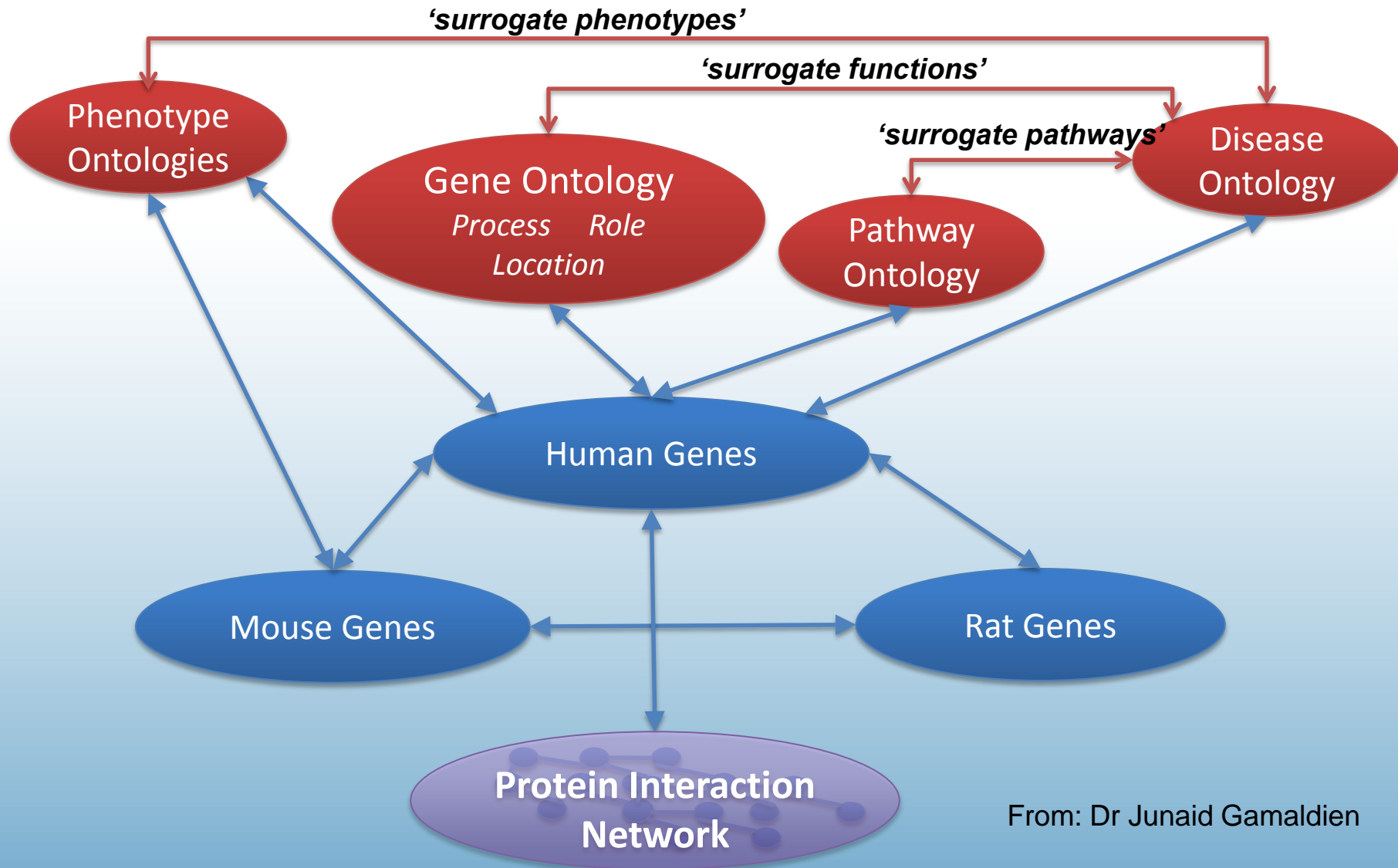


- Exome sequence $> \pm 70$ million reads, 100bp per read
- Alignment to Human Reference genome (3.2 billion bps)

- **Total number of SNPs = 39316**
- missense SNVs = 10800
- SNVs in splice sites = 40
- SNVs in coding synonymous = 11450
- SNVs near a gene = 158
- intergenic SNVs = 1745
- frameshift indels = 205
- indels in splice sites = 15
- indels near a gene = 21
- intergenic indels = 127

Prediction of Functional Variants using the **BORG**

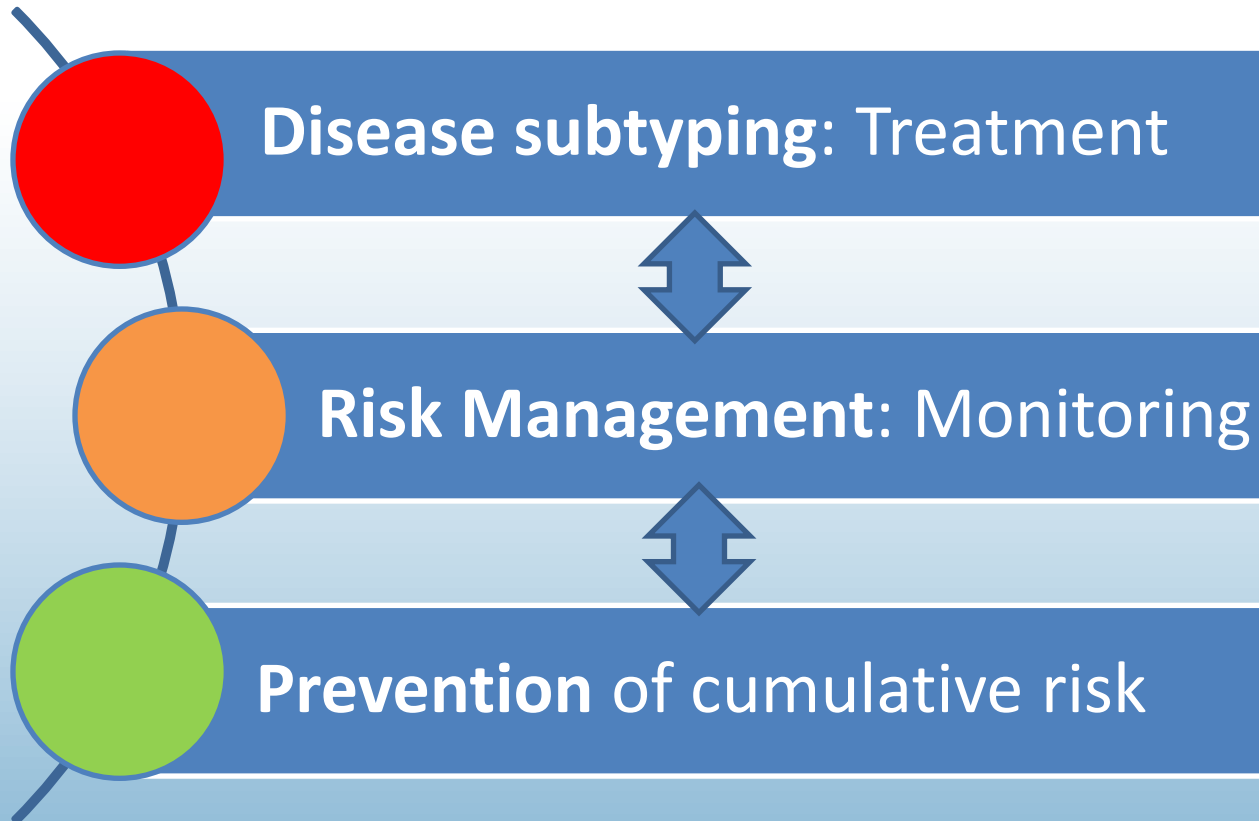
The **B**io**O**ntological **R**elationship **G**raph (B.O.R.G)



From: Dr Junaid Gamaldien

Models vast amounts of *existing* biomedical knowledge in a 'mind map' to uncover *novel* links between mutation(s) and disease

Gene-based intervention



Acknowledgements

- Team members, collaborators & students
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