

# Incremental Use of Genetics and Genomics of Cancers in Translational Medicine



Africa Health – Leaders Forum

**Raj Ramesar**

**MRC Research Unit For Genomic and Precision Medicine**

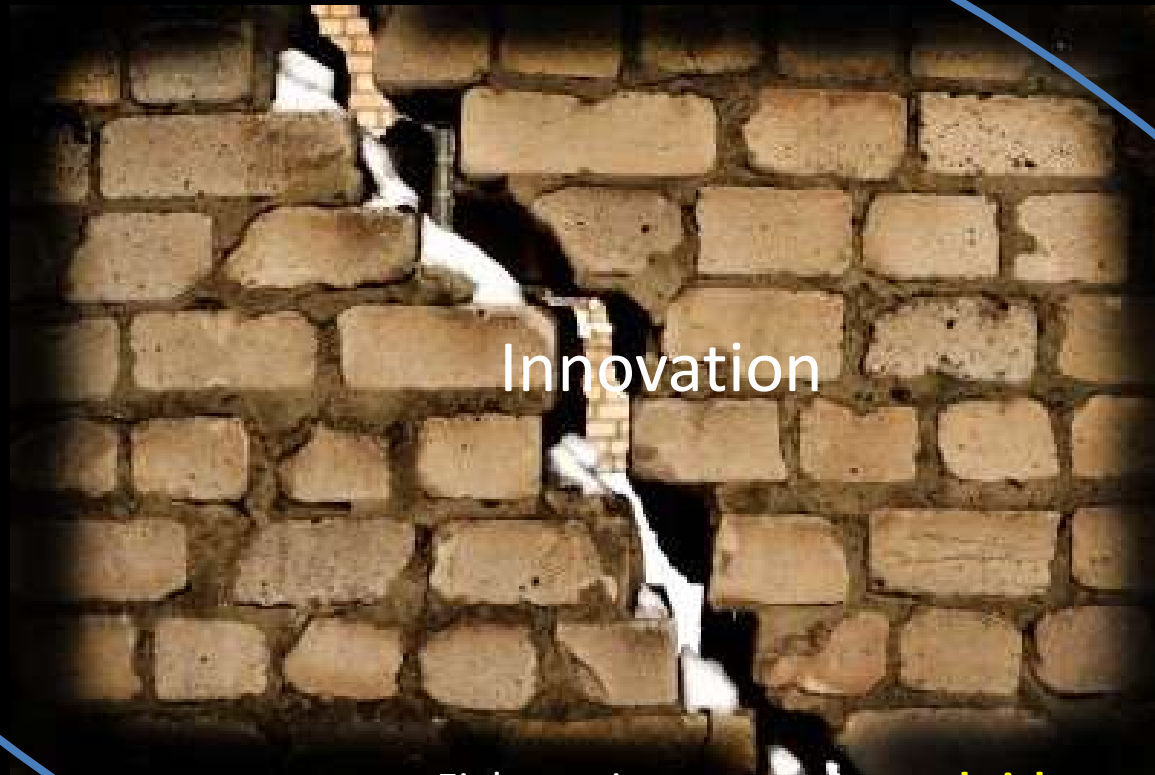
**Division of Human Genetics**

**Institute of Infectious Disease and Molecular Medicine**

**University of Cape Town and Affiliated Hospitals**



Research



Innovation

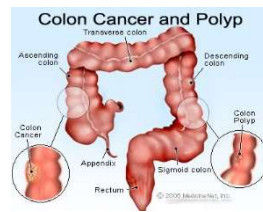
.....Fight against cancer is **one brick at a time,**  
perhaps to eventually see a crack of hope.....  
**every brick out is hope to somebody**.....

Translation





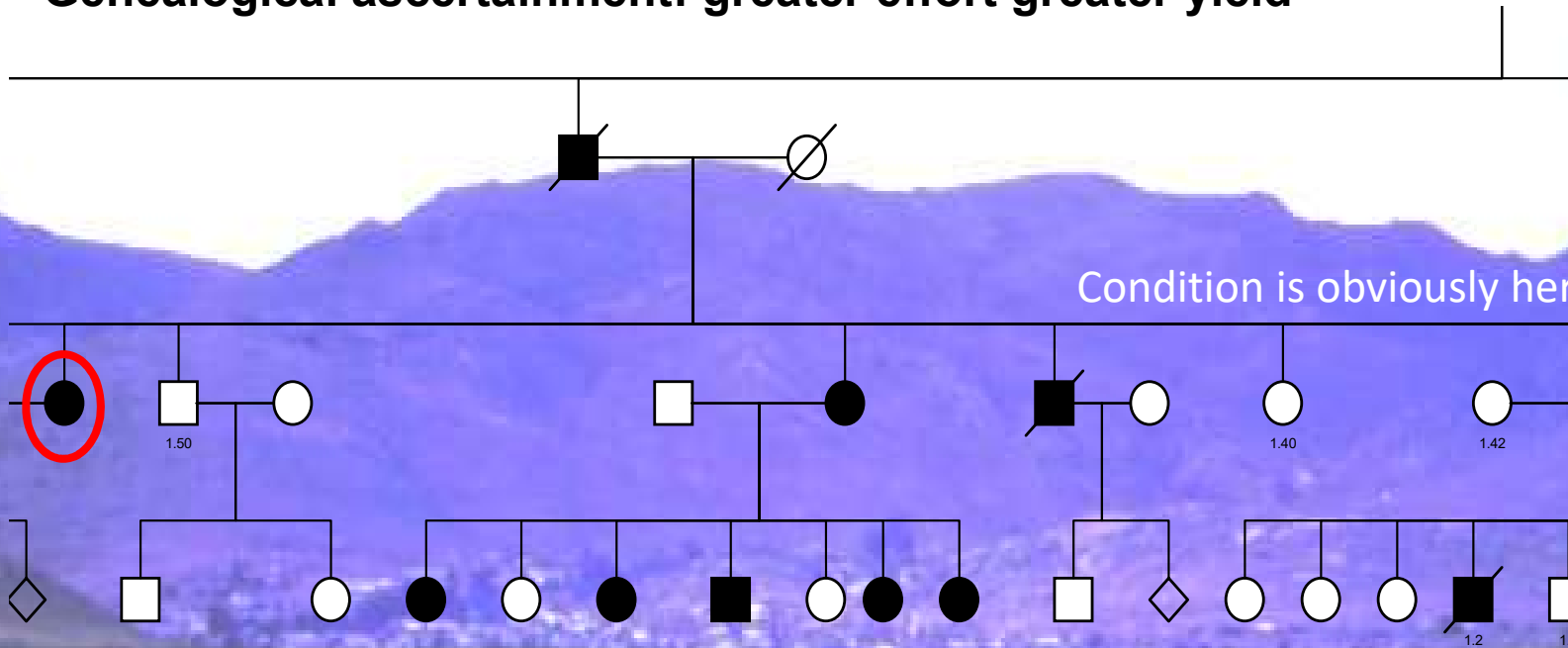
45 y.o. female  
Admitted to GSH  
Abdominal obstruction



consult:  
Diagnosis: tumour mass in ascending  
colon

Management: surgery/hemicolectomy

# Genealogical ascertainment: greater effort greater yield



Condition is obviously hereditary

Implications for clinical management and familial risk



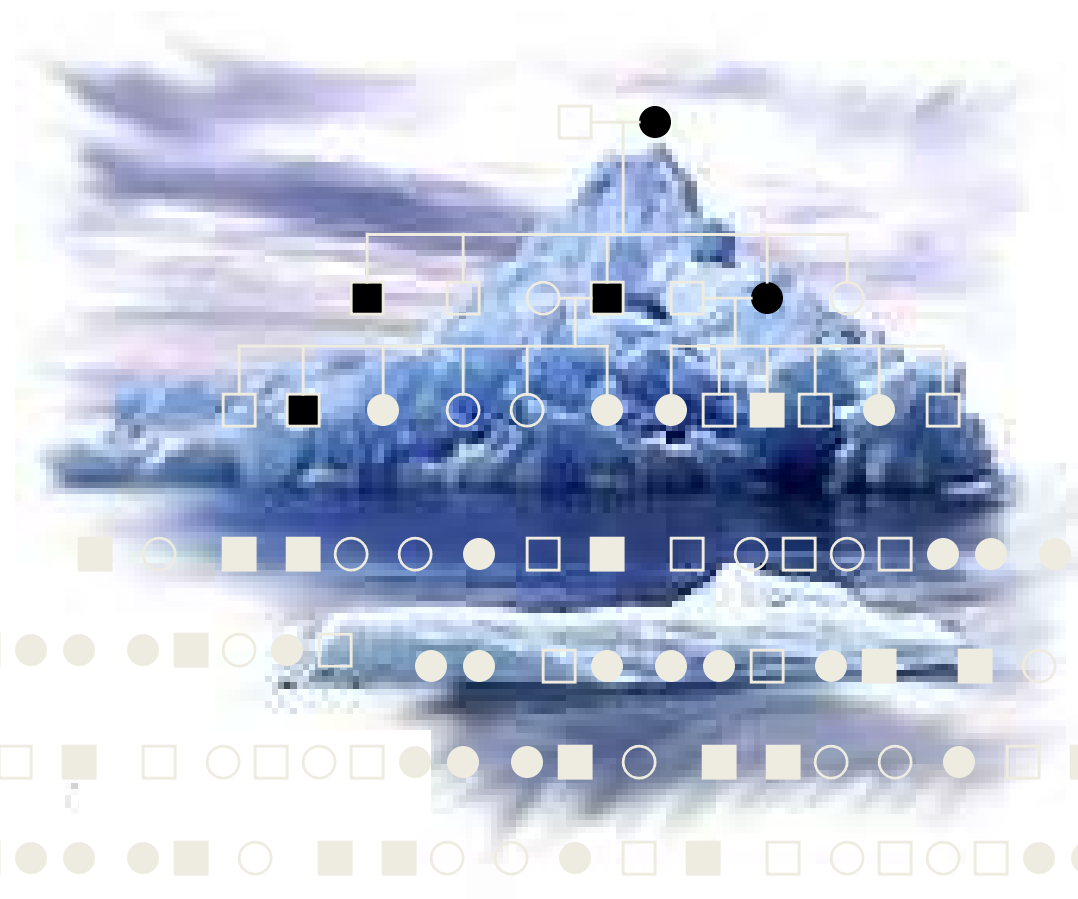
Field/community work – tracking families, raising awareness







Genetic Lineages extend to far flung areas of W and N Cape Provinces

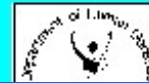


Recognition of empiric risk, genetic counselling,  
Surveillance colonoscopies





## UCT Molecular Genetics Laboratory



### Patient Data Main Form

#### Add/Edit Patient Information

Record No.  DNA Number  First Date

Surname  Other Name(s)

Reason  Disease Status  (Current status)

DOB  Sex  Ethnic Group  Inheritance

More Patient Info | Family | Sample Details | Management | Genotyping | Mutation Detection | Diagnostic | Clinical NPC

|   | Date       | DiagnosisAge | SiteOfCancer     | Colonoscopy                         | Upper Scope                         |
|---|------------|--------------|------------------|-------------------------------------|-------------------------------------|
|   | 1992/10/05 | 57           | sigmoid + rectum | <input checked="" type="checkbox"/> | <input type="checkbox"/>            |
|   | 1993/10/14 |              |                  | <input checked="" type="checkbox"/> | <input type="checkbox"/>            |
| * |            |              |                  | <input checked="" type="checkbox"/> | <input checked="" type="checkbox"/> |

Show Surgery

Change View

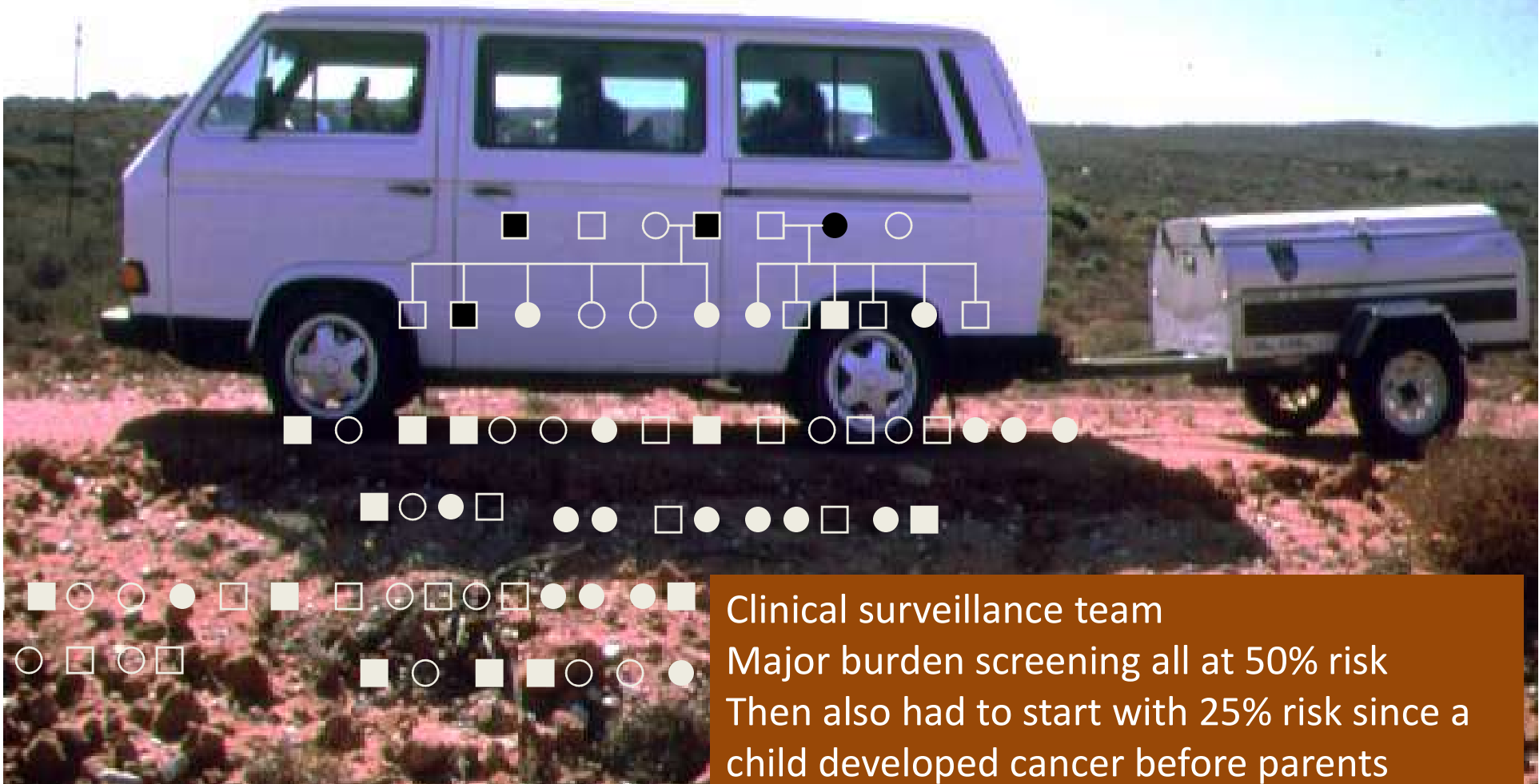
Simple well developed database  
 And family trees showing risk,  
 Testing status, counselling status,  
 As well as details of clinical surveillance,  
 And pathologies

Exit

Record:       of 2

- Records**
- Add New Record
  - Add/Edit Patient Data
  - Clinical RDD Data
  - Edit/Browse Minimal Records
  - Edit Full Menu
  - Browse Full

Recognition of empiric risk, genetic counselling,  
Surveillance colonoscopies



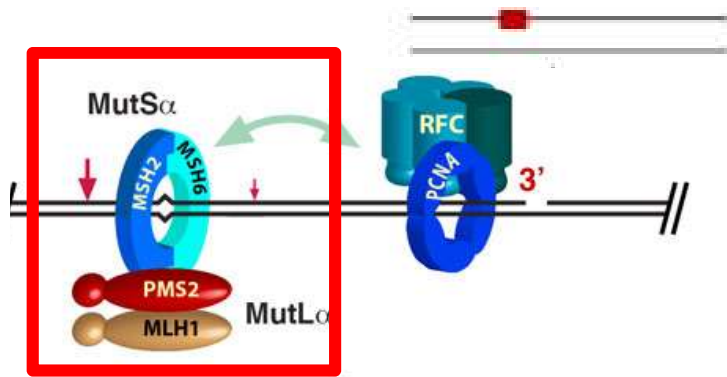




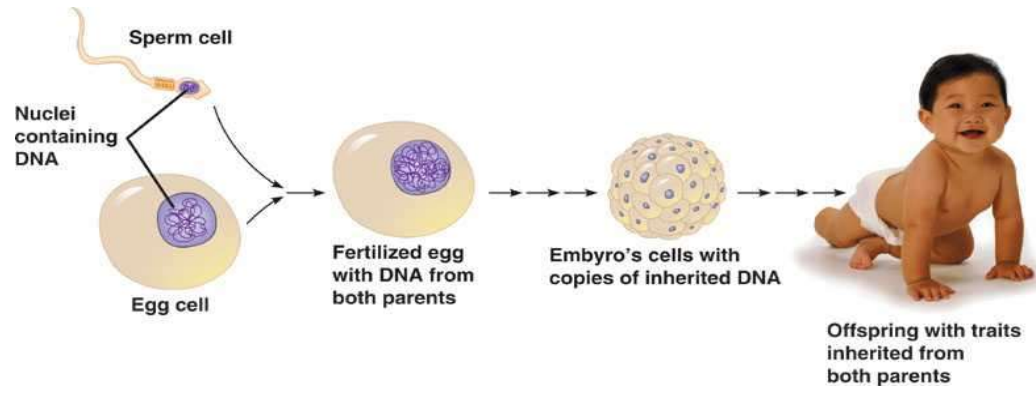
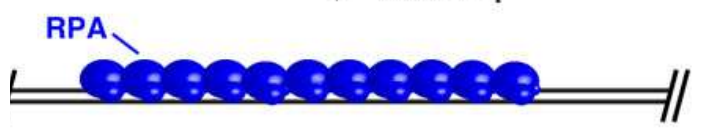
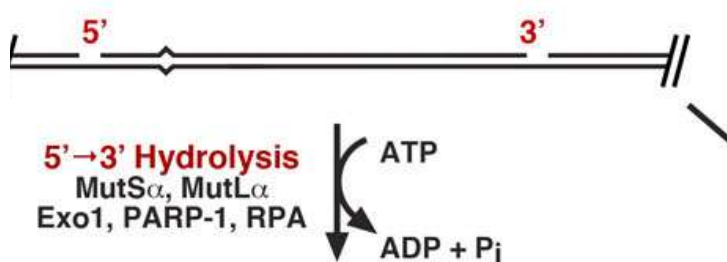
Prof Paul Goldberg

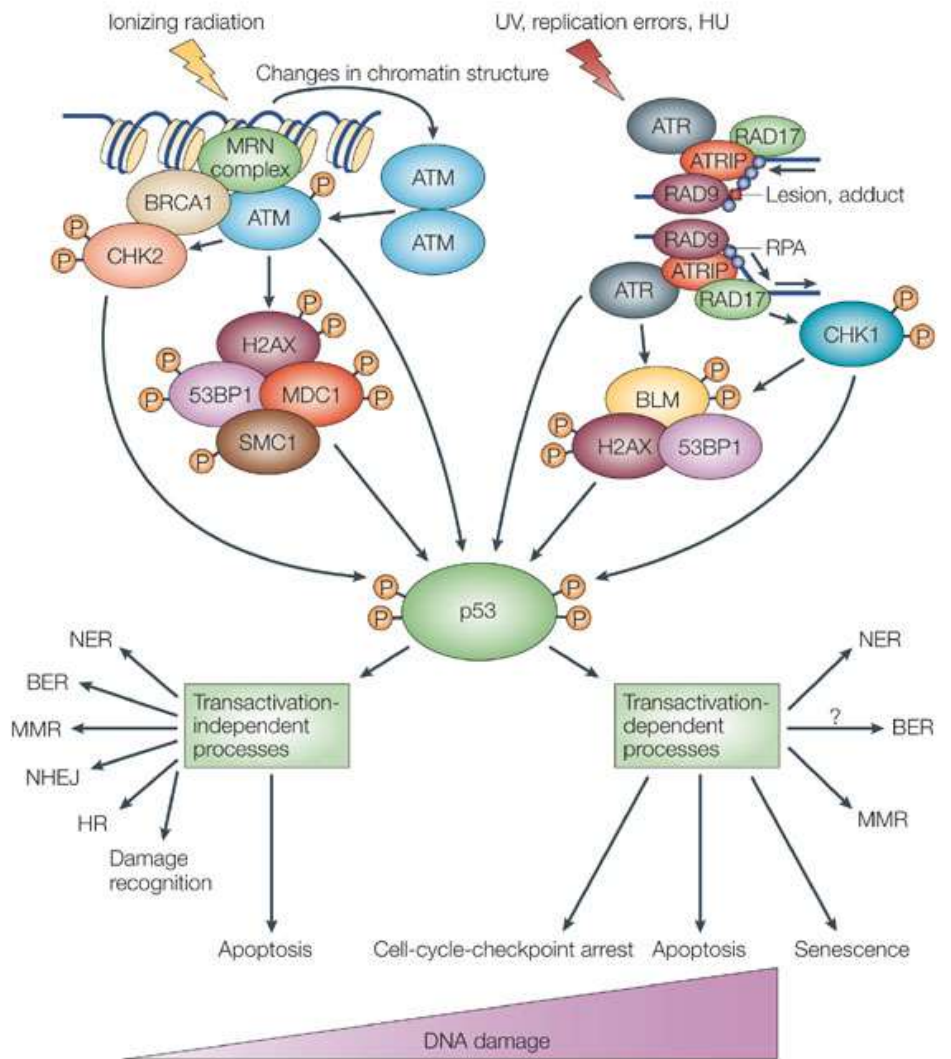
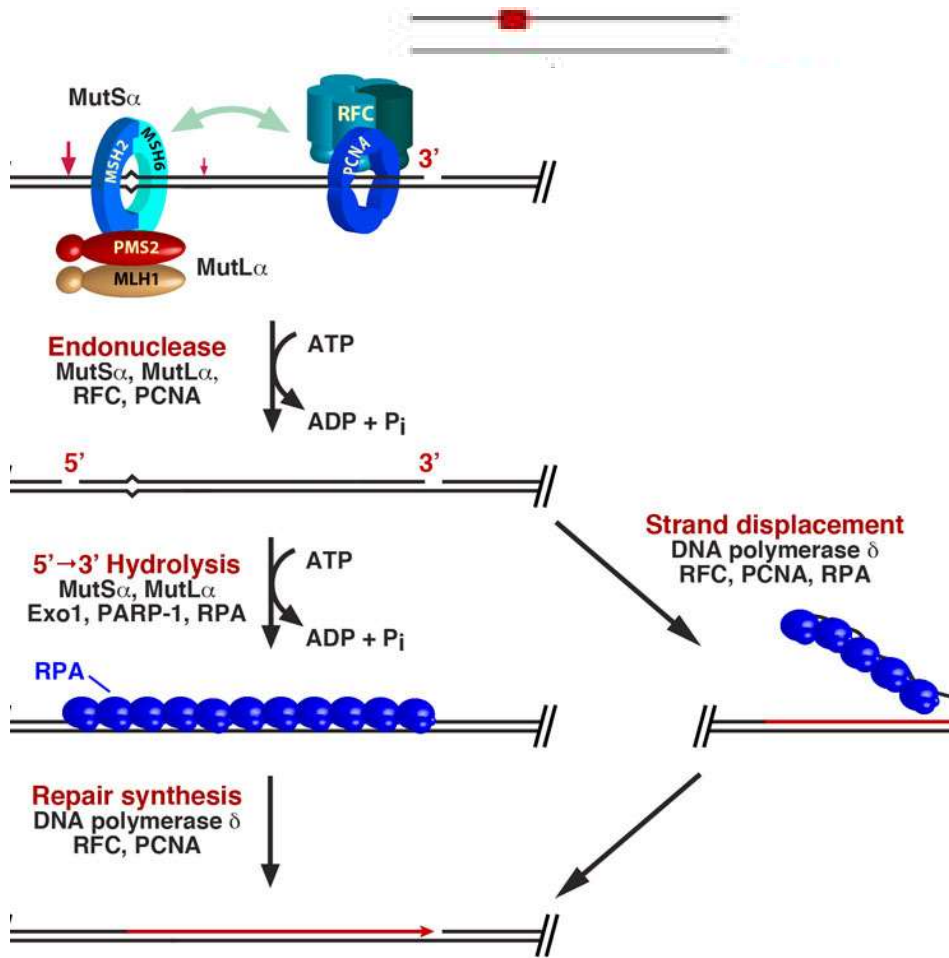
Sr Ursula Algar



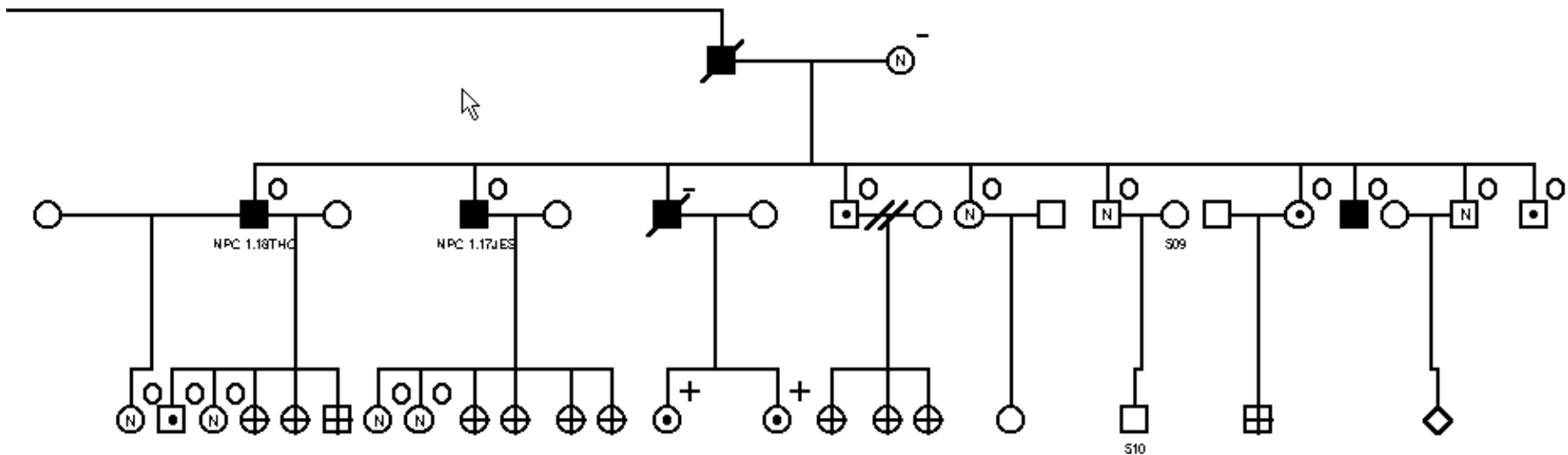
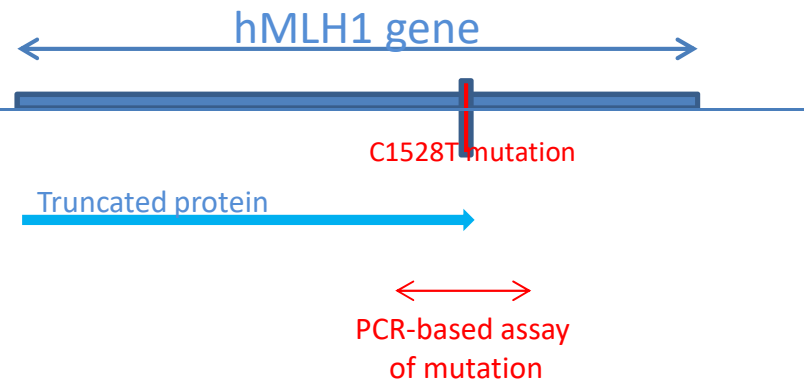


During cell replication –  
 $3.5 \times 10^9$  base pairs have to be replicated with a high degree of fidelity  
 Post replication repair complex system








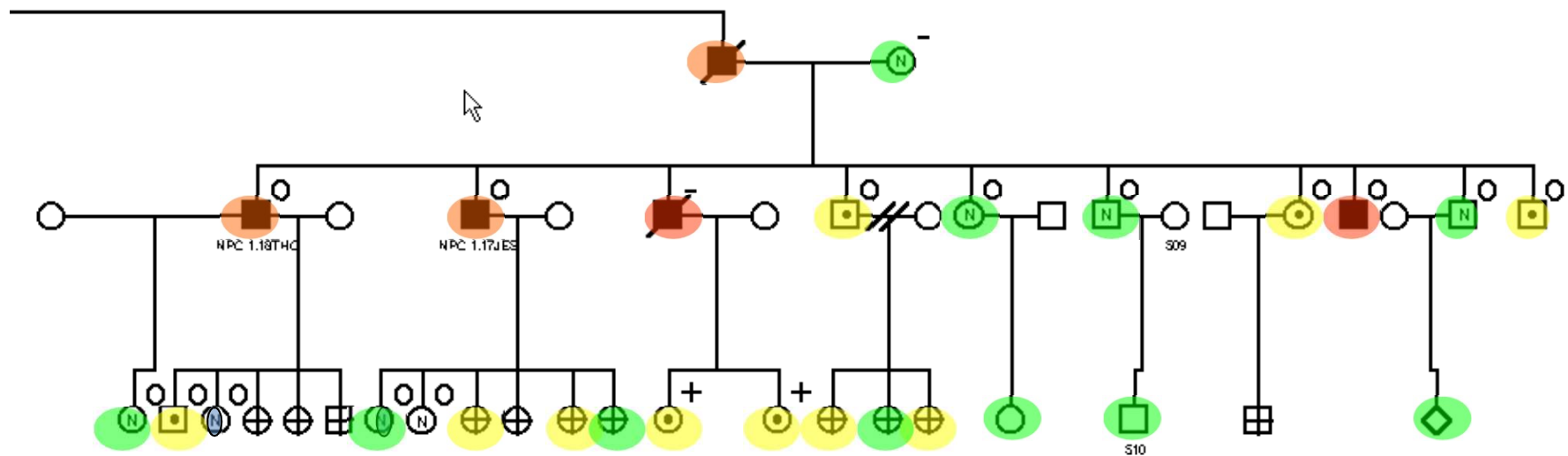
Discovery led to simple PCR-based test  
For the mutation



Many such families are currently being clinically managed between Human Genetics (genetic counselling and genetic testing) and Surgical Gastroenterology (clinical surveillance)

Discovery led to simple PCR-based test  
For the mutation

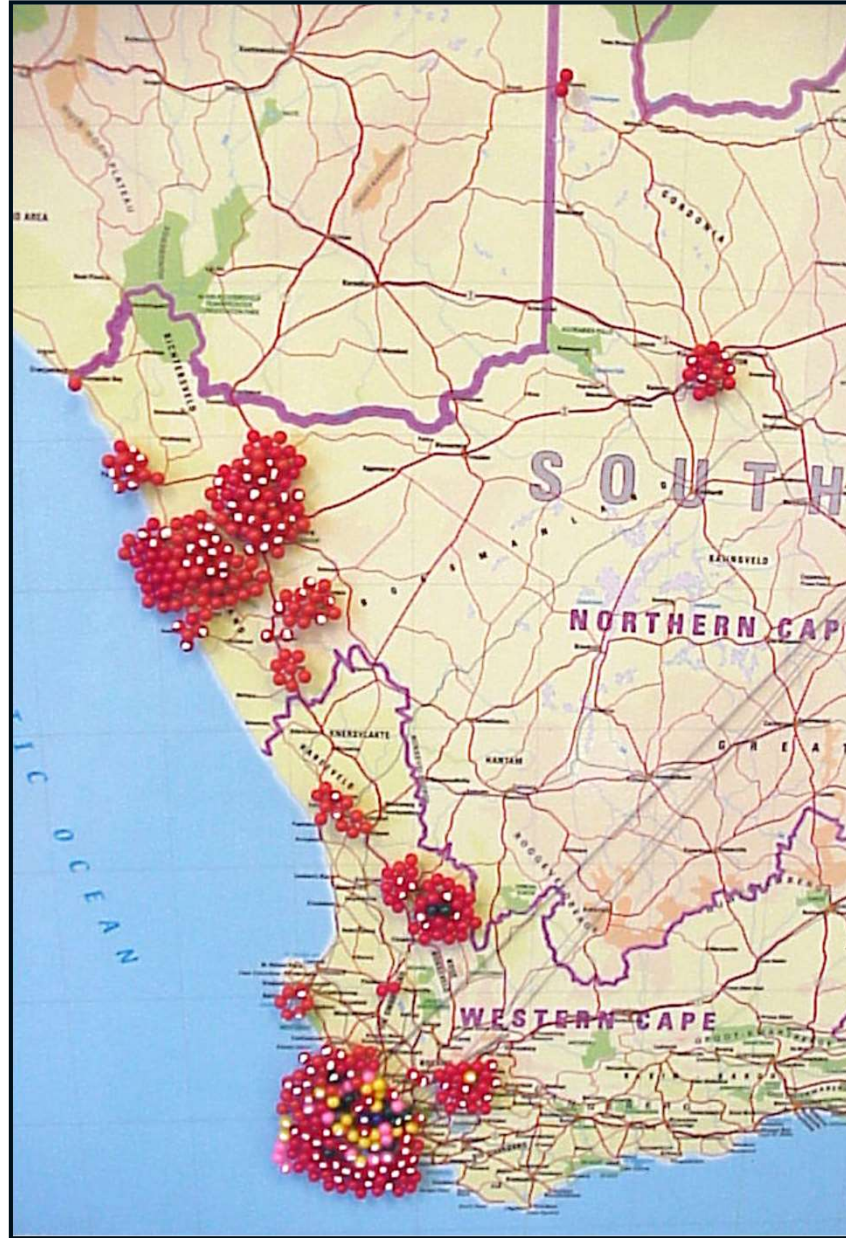
-  **Affected** with mutation  
Risk 100%
-  **Unaffected** with mutation  
Risk 80-90%
-  **Unaffected:** No mutation  
risk 0%



Many such families are currently being clinically managed between  
Human Genetics (genetic counselling and genetic testing)  
and Surgical Gastroenterology (clinical surveillance)



**hMLH1  
C1528T  
mutation**

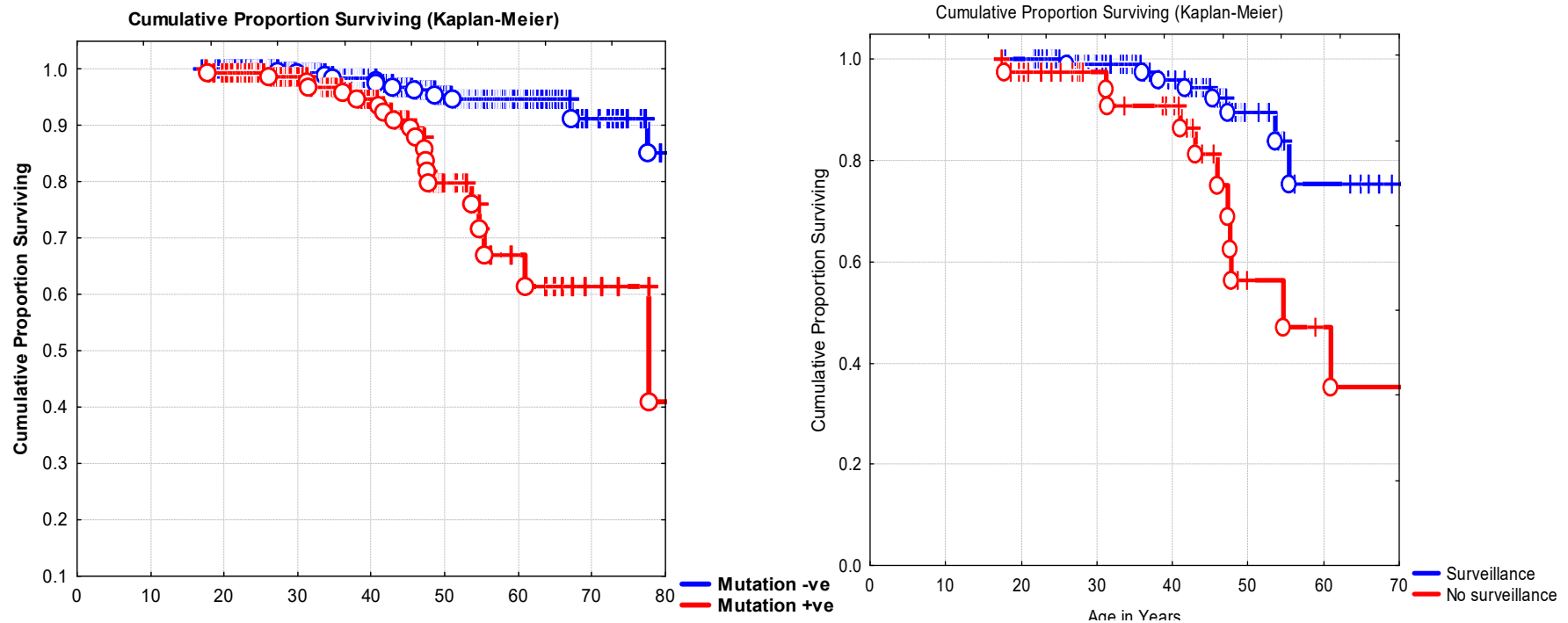


# Surveillance colonoscopy improves survival in a cohort of subjects with a single mismatch repair gene mutation

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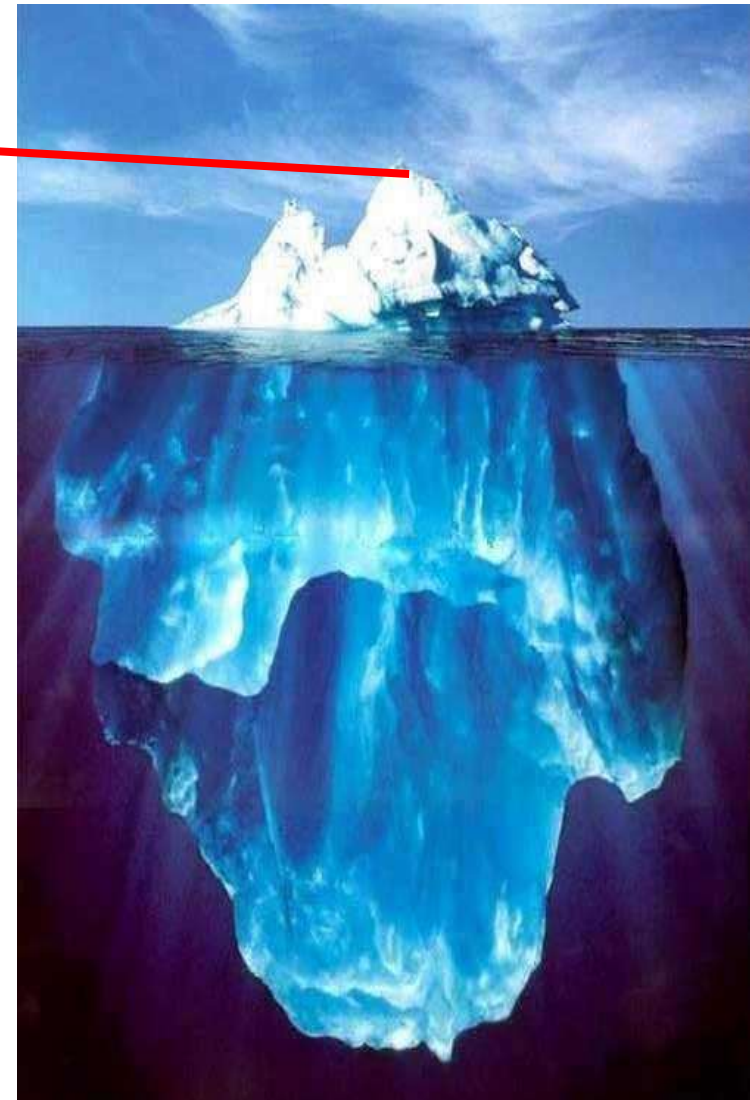


Large scale screening of structural genes  
hMLH1, hMSH2 and hMSH6

Screening of MMR genes in all  
<50 y of age

| SAMPLE               | SITE      | NUCLEOTIDE POSITION     | AMINO ACID POSITION      |
|----------------------|-----------|-------------------------|--------------------------|
| <b>MUTATIONS</b>     |           |                         |                          |
| <i>hMSH2</i>         |           |                         |                          |
| ● NPC 85.1, 107.1    | Exon 6    | G965A**                 | G322D                    |
| NPC 45.1             | Exon 6    | C1046G                  | P349R                    |
| NPC 120.1            | Exon 7    | 1220delCT               | Frameshift               |
| NPC 5.6              | Exon 8    | 1340insGG               | Frameshift               |
| NPC 42.1             | Exon 9    | A1489G                  | I497V                    |
| NPC 145.2            | Exon 15   | 2501delCTAATT           | Frameshift               |
| <i>hMLH1</i>         |           |                         |                          |
| NPC 85.1             | Exon 4    | C350T**                 | T117M                    |
| NPC 43.1             | Exon 6    | G→A 5' donor site + 3** | Total skipping of exon 6 |
| NPC 15.1             | Exon 9    | 731delGTGA              | Frameshift               |
| NPC 94.1             | Exon 13   | 1521insT                | Frameshift               |
| ● NPC 1.2            | Exon 13   | C1528T                  | Nonsense                 |
| NPC 26.2, 121.1      | Exon 19   | C2152T                  | H718Y                    |
| <i>hMSH6</i>         |           |                         |                          |
| NPC 101.1            | Exon 4    | T2633C**                | V878A                    |
| <b>POLYMORPHISMS</b> |           |                         |                          |
| <i>hMSH2</i>         |           |                         |                          |
| 1 individual         | Intron 12 | IVS12-6T→C              | -                        |
| 2 individuals        | Exon 3    | C402T                   | I150I                    |
| <i>hMLH1</i>         |           |                         |                          |
| ● 1 individual       | Intron 4  | IVS4-41A→G              | -                        |
| 9 individuals        | Exon 8    | A655G**                 | I219V                    |
| 22 individuals       | Intron 14 | IVS14-19A→G**           | -                        |
| 1 individual         | Exon 19   | T2184C                  | Y721Y                    |
| <i>hMSH6</i>         |           |                         |                          |
| ● 17 individuals     | Intron 2  | IVS2+52T→A**            | -                        |
| 20 individuals       | Intron 4  | IVS4-56C→T              | -                        |
| 3 individuals        | Intron 4  | C1164T**                | H366H                    |
| 4 individuals        | Intron 4  | C1869T                  | P623P                    |
| 14 individuals       | Intron 7  | IVS7-51del3647-3651     | -                        |

\*\* mutation previously described in the literature



How do we get to all those in need?

**Genetics + Family Medicine**



RESEARCH CAPACITY

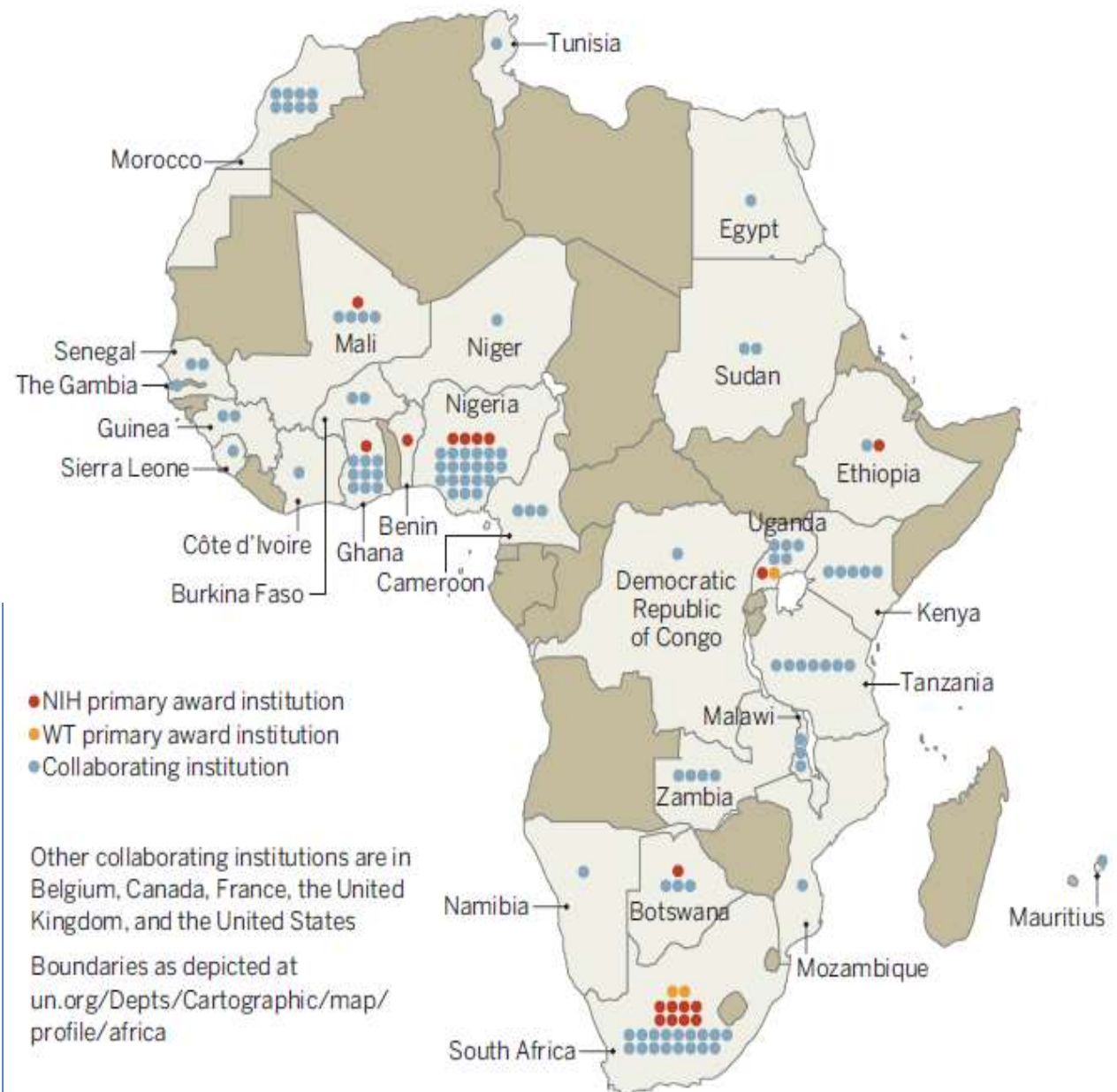
# Enabling the genomic revolution in Africa

H3Africa is developing capacity for health-related genomics research in Africa

By The H3Africa Consortium\*†

## National Institutes of Health Wellcome Trust H3Africa Research Network

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Thank you