

Genetics and Lynch syndrome

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Living with Lynch syndrome
12th September 2015

What is Lynch syndrome?

- Cancer predisposition condition:
 - **Colorectal (CRC)**
 - **Endometrial**
 - **Ovarian**
 - **Urothelial**
 - Gastric
 - Small bowel
 - Hepatobiliary tract
 - Pancreas
 - Brain
 - Multiple sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas
- Most common hereditary CRC predisposition syndrome

Historical aspects



- 1895 Dr Aldred Warthin (pathologist University of Michigan) noted his seamstress appeared depressed
- “I’m healthy now, but I fully expect to die an early death”



HEREDITY WITH REFERENCE TO CARCINOMA

AS SHOWN BY THE STUDY OF THE CASES EXAMINED IN THE PATHOLOGICAL
LABORATORY OF THE UNIVERSITY OF MICHIGAN,
1895-1913 *

ALDRED SCOTT WARTHIN, M.D.
ANN ARBOR, MICH.

The statistical study of carcinoma is regarded by many writers as having been carried as far as it can be profitable; and certainly but little that is new has been gained through this method during the last decade. Nevertheless, its possibilities have not been exhausted; and it is highly desirable that the whole neoplasm problem in all of its aspects be attacked again from the statistical standpoint, though in a somewhat different way. Practically all of the old statistical studies of neoplasms, particularly those of carcinoma, were based on mortality reports; or if not on these, on morbidity reports based on clinical diagnoses. In very few instances only has the statistical study been carried out on the basis of the records of a diagnostic pathological laboratory. Statistics of neoplasm from such a source must be of infinitely greater value than those founded on mortality statistics. In the records of the diagnostic laboratory the diagnosis is based on the histological examination, and the percentage of error is reduced to a minimum. In the mortality statistics, on the other hand, the diagnoses are chiefly clinical, and consequently subject to the wide error inherent in the clinical diagnosis of "tumor," neoplasm, "cancer" and the like. Moreover, the material coming to the diagnostic laboratory is usually seen from two to five years earlier than the mortality age. In studies relating to the age-incidence of any form of neoplasm it is evident that the records of the pathological laboratory for that neoplasm will be much more trustworthy than the mortality statistics. It is also possible many times in the diagnostic laboratory to follow the course of a neoplasm over a definite period, so that important practical knowledge may be gained as to rate of growth, recurrence, healing, metastases, etc.

The following study of the influence of heredity on carcinoma is taken from the records of the pathological laboratory of the University of Michigan during the years of my service from 1895 to 1913. During this period 3,600 cases of neoplasm of all varieties have been studied, either in material taken for practical diagnosis or obtained by necropsy. Of these 3,600 cases, some 1,600 were cases of carcinoma, as was shown by the microscopic diagnosis. Practically every variety of carcinoma

* Submitted for publication Aug. 8, 1913.

THE FURTHER STUDY OF A CANCER FAMILY

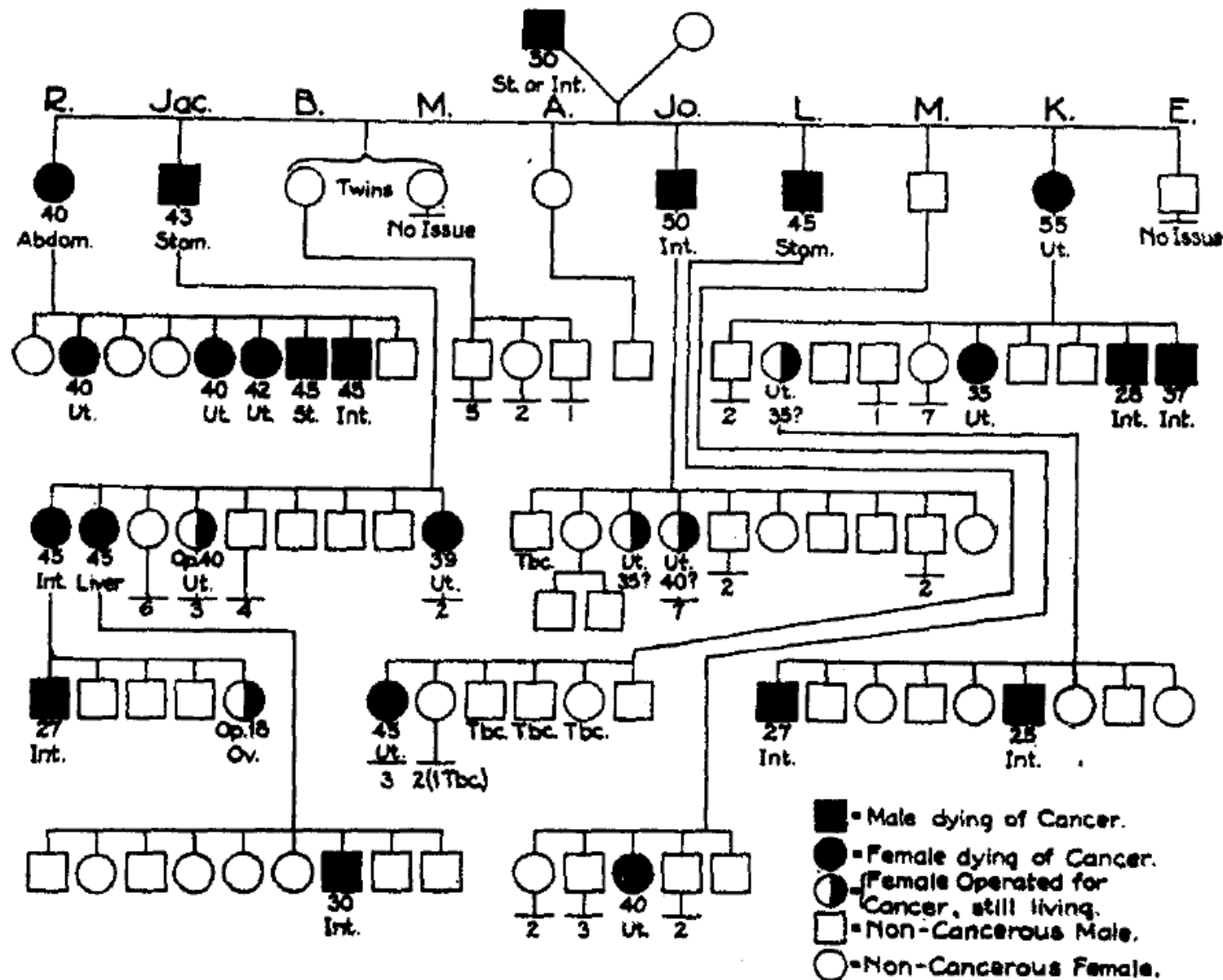
ALDRED SCOTT WARTHIN

*Professor of Pathology and Director of the Pathological Laboratory,
University of Michigan, Ann Arbor*

In the *Archives of Internal Medicine*, November, 1913, Vol. 12, pages 546-555, the writer reported a study of "Heredity with Reference to Carcinoma" based upon the cases of carcinoma examined for diagnostic purposes in the Pathological Laboratory of the University of Michigan during the period of 1895-1913. This statistical study, the facts of which were drawn from the relatively incomplete surgical histories accompanying the operative material, revealed a surprisingly high number of cases showing in the family history a multiple occurrence of carcinoma, in some cases so striking that the use of the terms "cancer family" and "cancer fraternity" was justified. This study seemed to show that a marked susceptibility to carcinoma exists in the case of certain family generations and family groups; that this susceptibility is frequently associated with a marked susceptibility to tuberculosis, and also with lowered fertility. The multiple occurrence of carcinoma in a family generation practically always was associated with its occurrence in a preceding generation; and the family tendency was found to be more marked when carcinoma occurred in both maternal and paternal lines. Family susceptibility to carcinoma was shown particularly in the case of carcinoma of the gastrointestinal tract and the uterus. In a family showing the occurrence of carcinoma in several generations there was shown a decided tendency for the neoplasm to develop at an earlier age in successive generations, and an especial degree of malignancy was often noted in such cases.

When this study was reported it met with little favor among surgical writers and particularly among those interested in propaganda for the prevention of cancer. In some of the

FAMILY G



Historical aspects



- 1962 Dr Henry Lynch looked after an alcoholic patient who drank because he knew he would die of colorectal cancer since everyone in the family died of colorectal cancer
- Lynch investigated further: colon cancer in absence of polyps, endometrial and ovarian cancers Family N (Nebraska)
- 1964 Dr Marjorie Shaw (geneticist) Family M (Michigan)
- Review of Family G: “Cancer Family Syndrome”
- Recognition of hereditary cancers and hope of improved detection and treatment

Hereditary Factors in Cancer

Study of Two Large Midwestern Kindreds

H. T. LYNCH, MD, OMAHA; M. W. SHAW, MD, ANN ARBOR, MICH;
C. W. MAGNUSON, MD; A. L. LARSEN, MD;
AND A. J. KRUSH, MS, OMAHA

Material and Methods

These two large families have been studied in Nebraska and Michigan and shall hereafter be referred to as the "N" (Nebraska) and "M" (Michigan) kindred.

MENDELIAN autosomal inheritance patterns have been demonstrated in familial aggregations of polyposis coli, retinoblastoma, xeroderma pigmentosum, neurofibromatosis,¹ Gardner's syndrome² and the basal cell nevus syndrome.³ In addition, an increased familial incidence of carcinoma of the breast,⁴ lung,⁵ stomach and colon,⁶ and prostate,⁷ as well as leukemia,⁸ multiple myeloma,⁹ Waldenström's macroglobulinemia,¹⁰ pheochromocytoma,¹¹ multiple endocrine tumors,¹² cerebellar hemangioblastoma,¹³ and malignant melanoma¹⁴ has been observed. However, the mode of inheritance is not clear in these latter conditions. In appraising these data, it must be kept in mind that only those families showing a high incidence of carcinoma are "selected" for publication. When one considers the high population incidence of carcinoma, "... it is bound to occur in excess in some families according to the operation of the laws of probability.¹⁵"

The purpose of this paper is to present the findings in two large midwestern kindreds in which a high frequency of particular histological types of malignant neoplasms involving a large variety of anatomical sites was found. In one kindred (Nebraska), there was a total of 51 malignant neoplasms of which 31 were confirmed, while in the second (Michigan) kindred, there were 27 carcinomas of which 20 were confirmed.

Received for publication Aug 6, 1965; accepted Oct 1. Read in part before the American Society of Human Genetics, Boulder, Colo., August 1964.

From the departments of internal medicine and pathology and the Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska College of Medicine, Veterans Administration Hospital, Omaha, and the Department of Human Genetics, University of Michigan Medical School, Ann Arbor.

Reprint requests to Eppley Institute, 42nd & Dewey Ave., Omaha, Neb 68106 (Dr. Lynch).

Arch Intern Med—Vol 117, Feb 1966

N Family.—The proband (No. U-11770) was studied at the Omaha Veterans Administration Hospital where he expired at age 44 from adrenal cortical carcinoma. His medical history revealed that many of his immediate relatives had cancer and that they lived over a wide geographic area. A questionnaire was sent to all adult members of the family in order to elicit information regarding a history of carcinoma and to obtain permission to examine surgical and autopsy material for histologic tissue confirmation. Permission forms were included with the questionnaire enabling us to make contact with family physicians, consultants, hospitals, state divisions of vital statistics, and local departments of public welfare. Several field trips were made, and clinic facilities were kindly donated by a private physician who had managed some of the affected members of the family. Complete histories and physical examinations, including pelvic examinations, cervical cytology, and proctosigmoidoscopy, were done on 35 individuals who resided in a contiguous geographic area. When lesions were accessible to surgical biopsy, appropriate tissue was obtained. Blood was obtained for ABO typing, hemoglobin, hematocrit, and cell indices.

M Family.—The proband (No. 945482) was studied at the University Hospital, Ann Arbor, Michigan, where she expired at age 36 from metastatic carcinoma of the breast. A strong family history of carcinoma had been elicited and similarly questionnaires were sent to members of the family. Histologic confirmation of carcinoma was made through physicians' records and pathology reports from several hospitals. In addition, cytogenetic studies were done on the proband prior to her death. These included karyotype analyses of leukocytes from two peripheral blood cultures, skin from the leg, and the pituitary gland following an ablation procedure.

Whenever possible, slides were personally reviewed from both families. In those cases showing

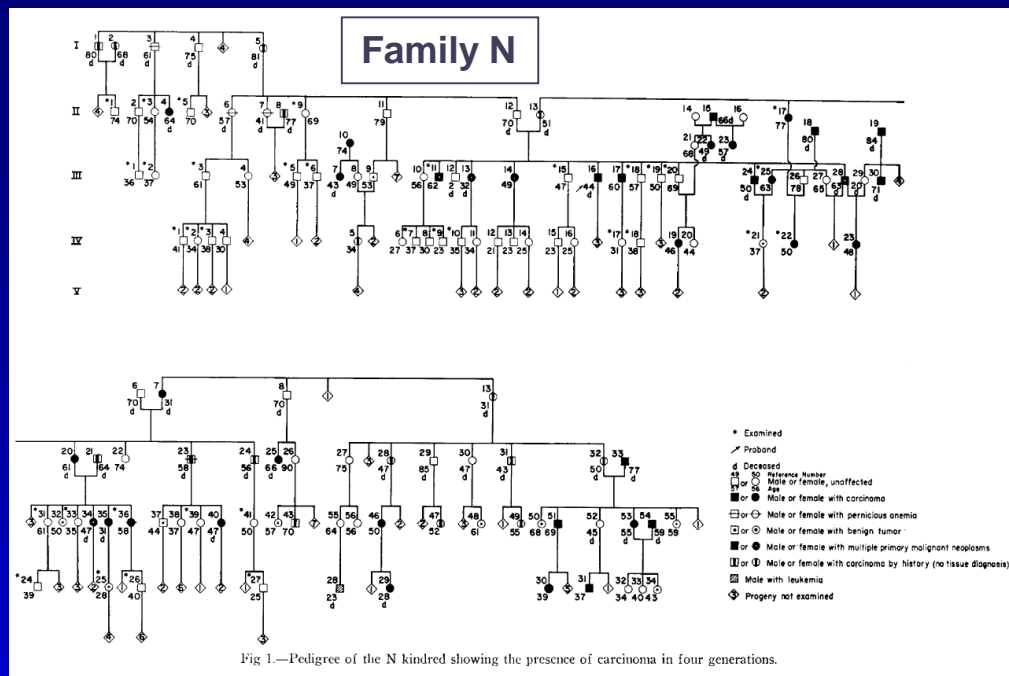


Fig 1.—Pedigree of the N kindred showing the presence of carcinoma in four generations.

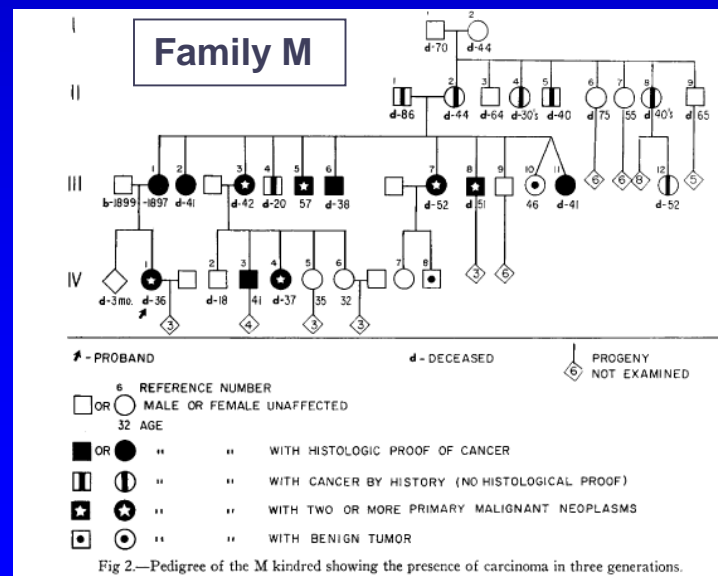


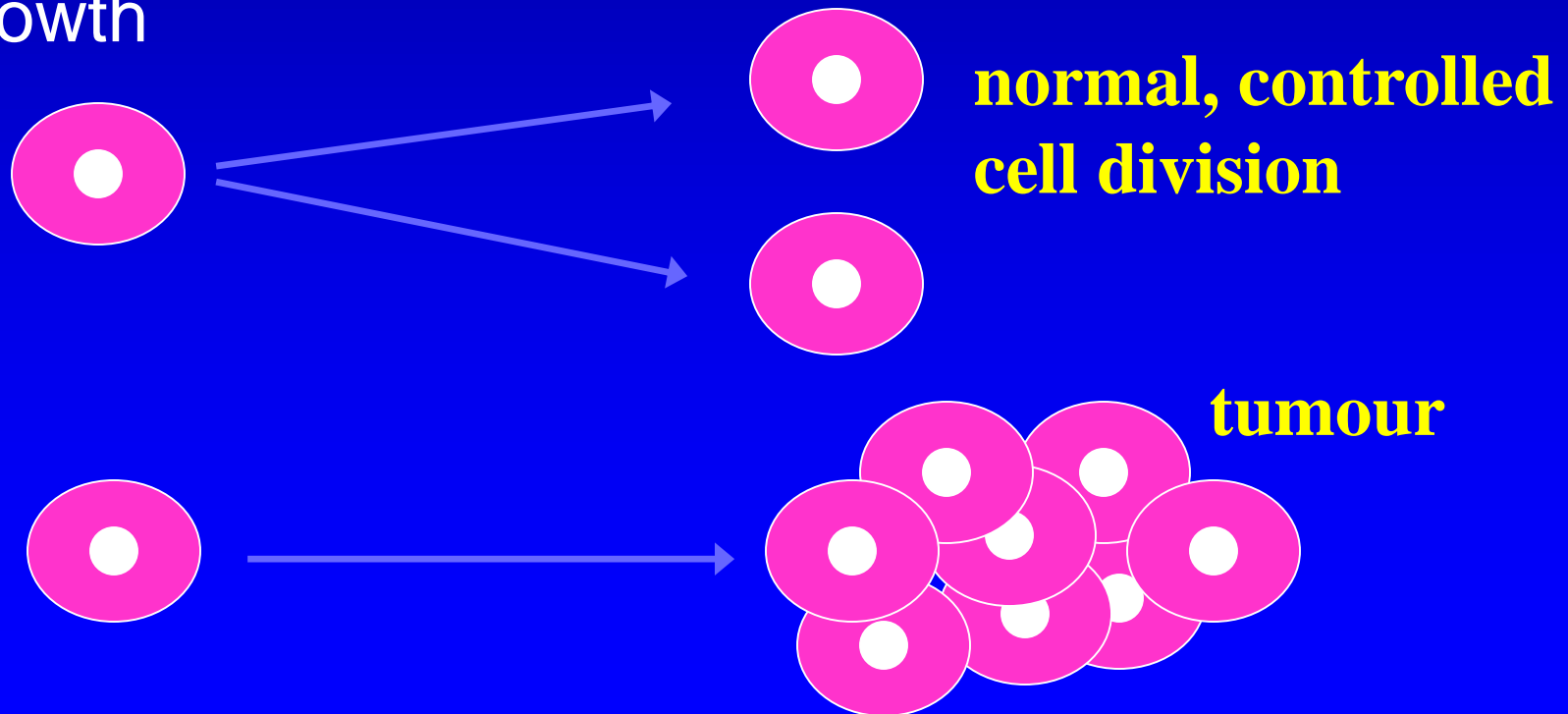
Fig 2.—Pedigree of the M kindred showing the presence of carcinoma in three generations.

Naming of a syndrome

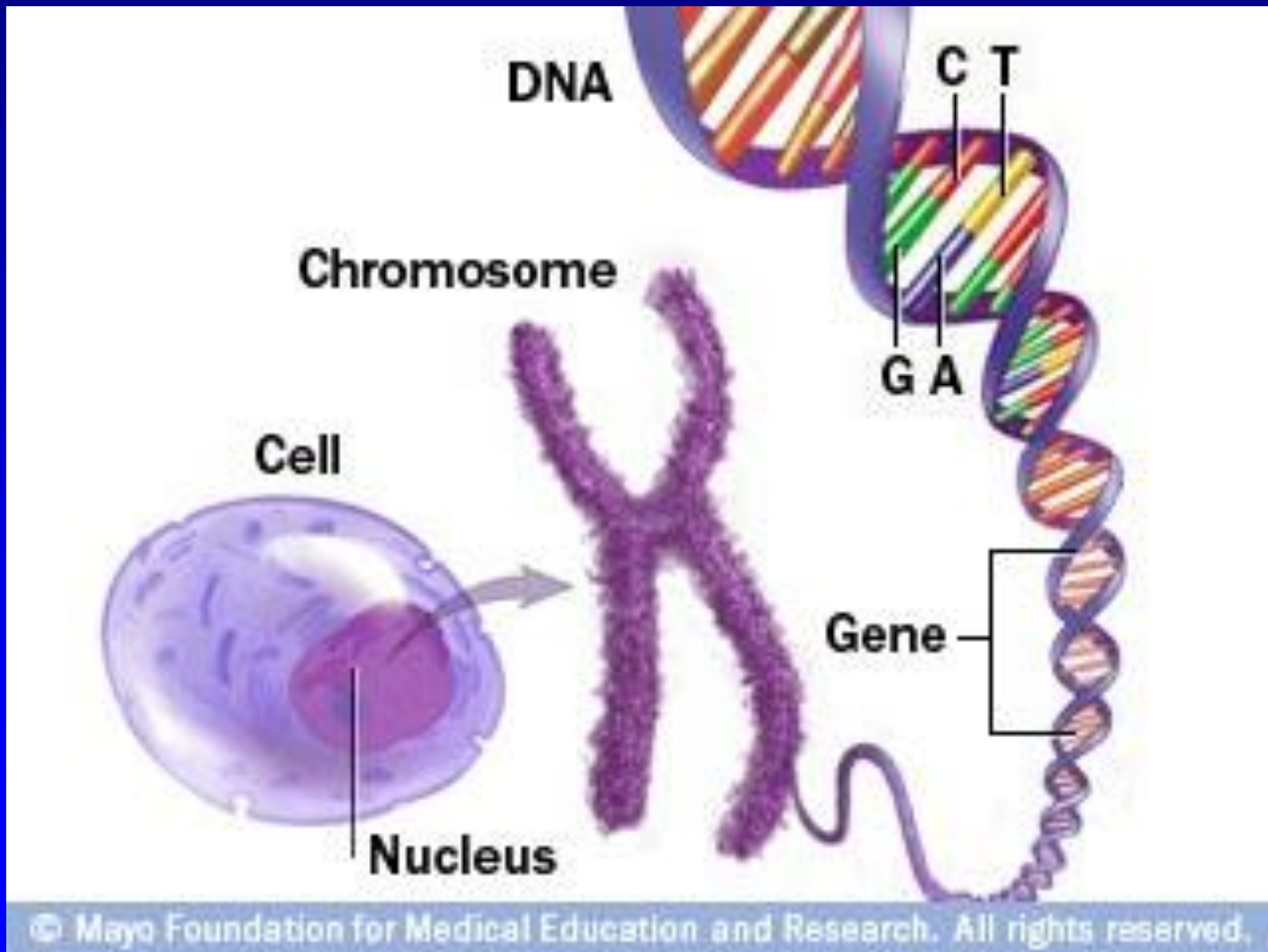
- 1913: Cancerous fraternities
- 1971: Cancer family syndrome
- 1984: Lynch syndrome I and II
- 1985: Hereditary Non Polyposis Colorectal Cancer (HNPCC)
- **Lynch syndrome**

Cancer

- Cancer is a common condition with approximately 1 in 3 people developing some form of cancer within their lifetime
- Cancer is caused by uncontrolled cell division and growth



Genes



Cancer

- Most cancers develop due to random faults (mutations) in growth control (cancer protection) genes in cells of the body
- These mutations are acquired during one's life (somatic mutations)
- Mutations can occur when cells are going through cell division or in response to environmental insults

Cancer



Hormones

Age



Smoking



Alcohol



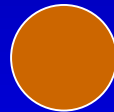
UV



Diet

Environmental

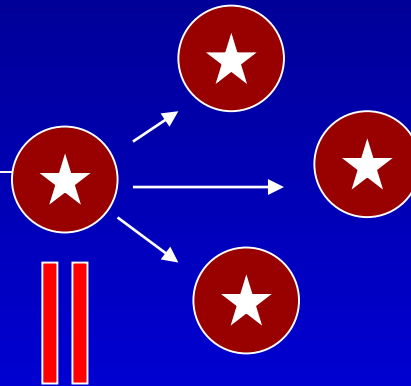
Influences



One functioning gene



Two functioning genes

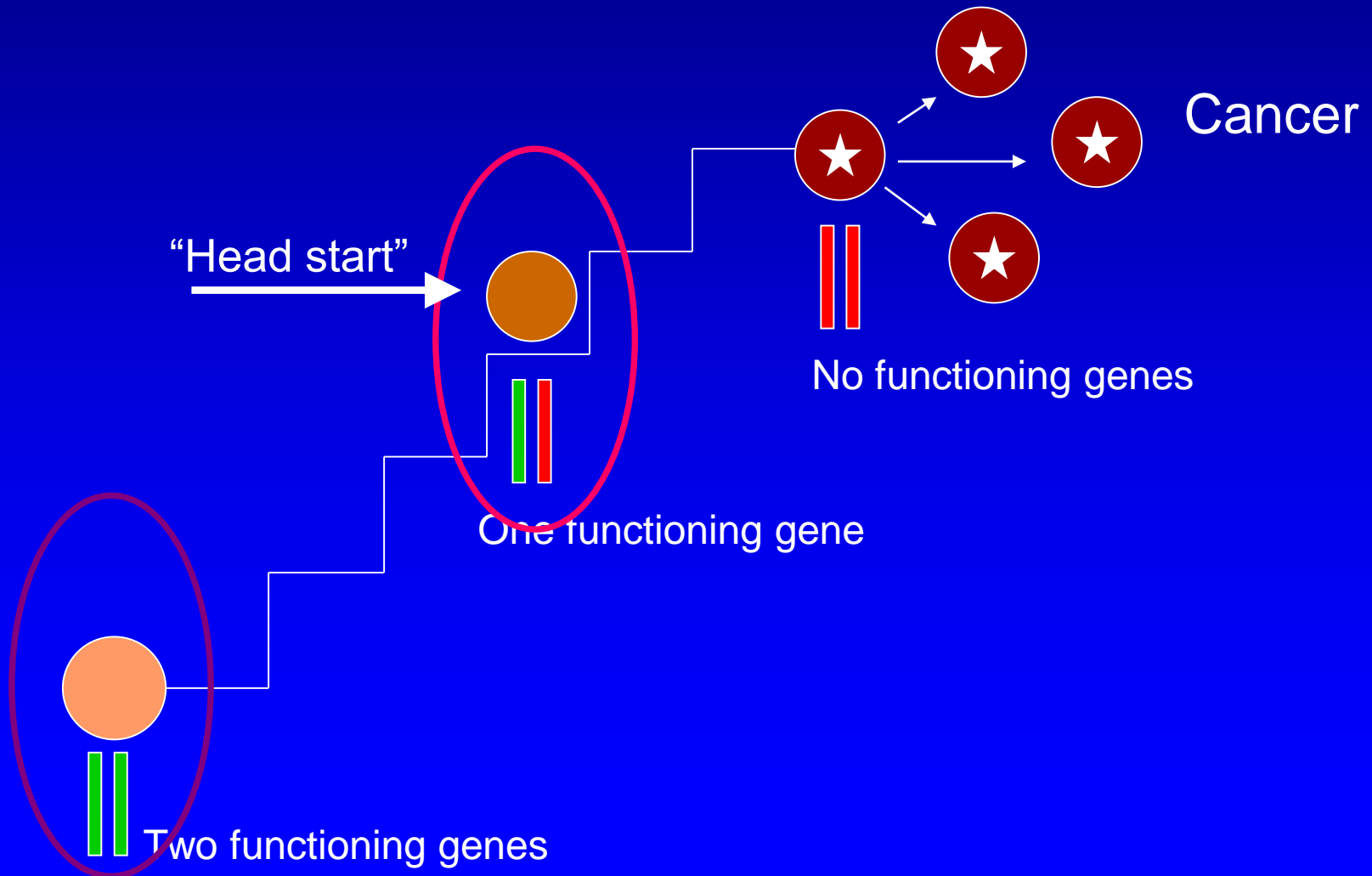


No functioning genes

Cancer

- These somatic mutations are not passed to offspring
- Hereditary cancer results from a germline mutation (it is present in all cells from birth), and can be passed on from one generation to the next

Cancer

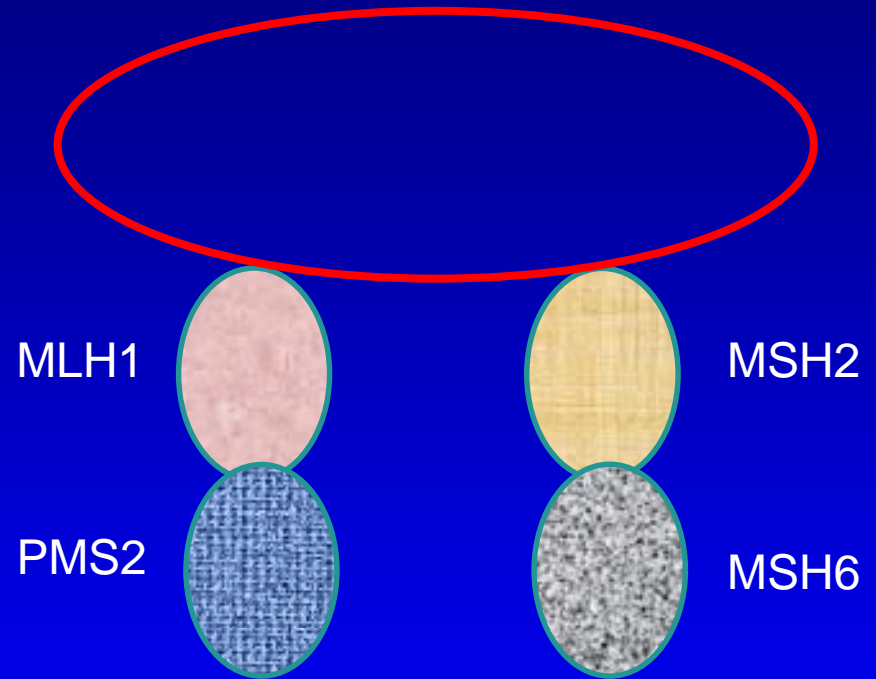


What causes Lynch syndrome?

- Mutation in a mismatch repair (MMR) gene:
 - *MSH2* (1993)
 - *MLH1* (1994)
 - *PMS2* (1994)
 - *MSH6* (1997)
 - *EPCAM* (2009)

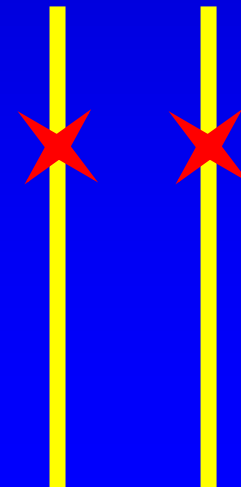
MMR genes

- MMR gene instructs body to make MMR protein
- MMR proteins function in pairs that recognise and repair mistakes in the DNA (genes)



MMR genes

- Lynch syndrome:
born with a mutation
in 1 of a person's 2
copies of MMR gene
- In a tissue, 2nd copy
develops a mistake,
meaning cell is unable
to make MMR protein

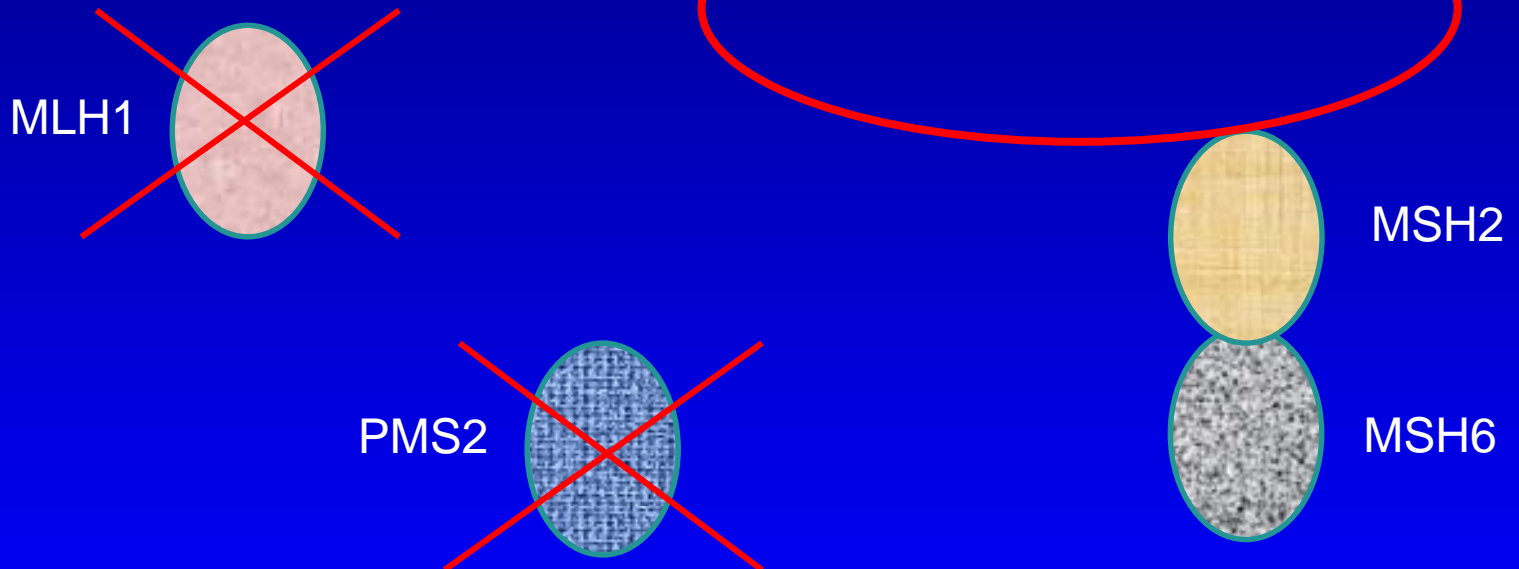


MMR genes

- Cell develops genetic destabilisation with an increased rate of mutations in many genes, often in regions called microsatellites
- Hence Lynch syndrome associated cancers are often found to have “microsatellite instability” (MSI)
- Leads to uncontrolled cell growth: cancer

MMR genes

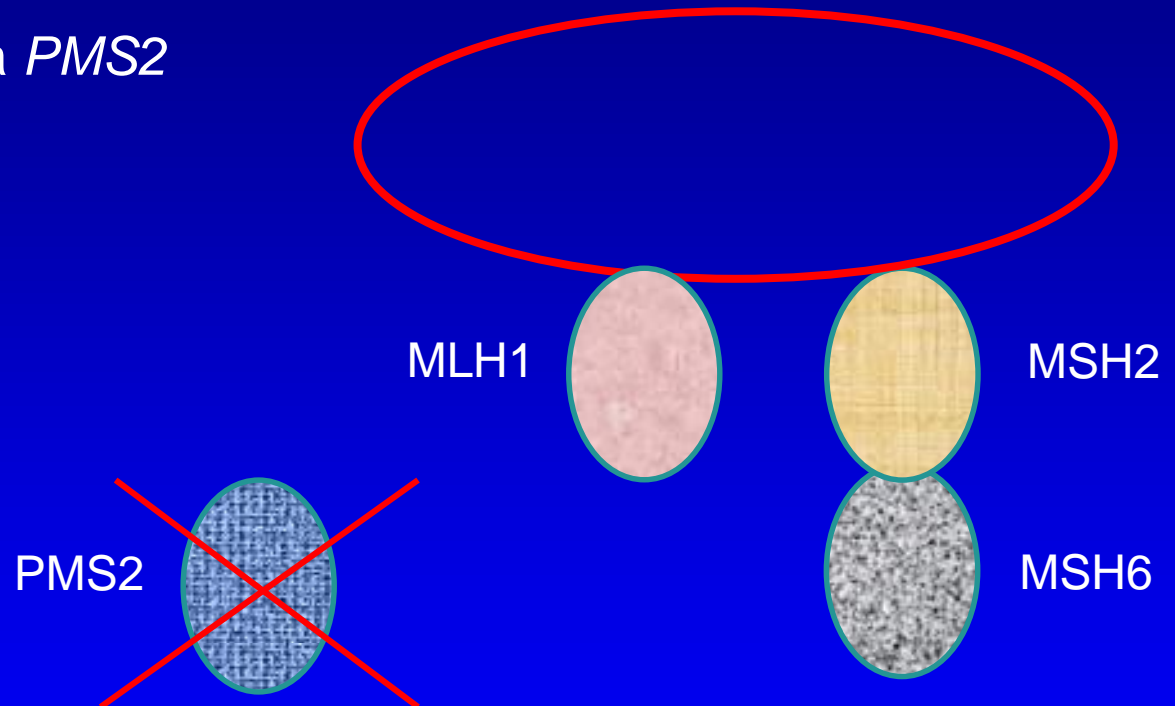
- For example with an *MLH1* mutation:



Immunohistochemistry (IHC) test shows loss of MLH1 and PMS2 proteins

MMR genes

- For example with a *PMS2* mutation:



Immunohistochemistry (IHC) test shows loss of PMS2 protein only

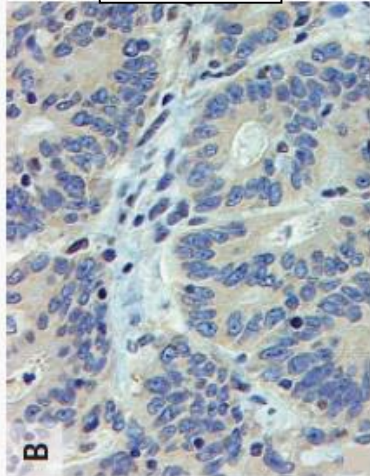
IHC patterns

Gene mutation	IHC
<i>MLH1</i>	MLH1 + PMS2 loss
<i>MSH2</i>	MSH2 + MSH6 loss
<i>MSH6</i>	MSH6 loss
<i>PMS2</i>	PMS2 loss

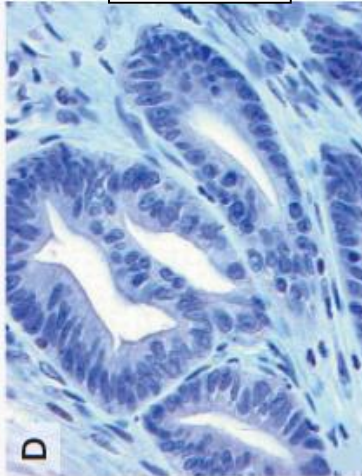
MMR immunohistochemistry (IHC)

Lynch
syndrome

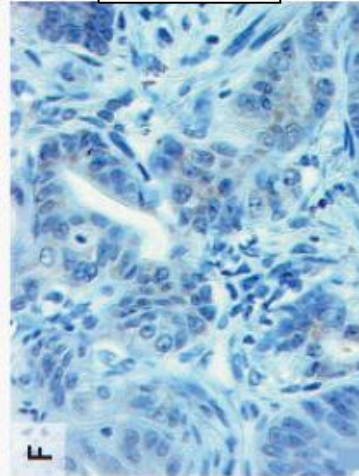
MLH1



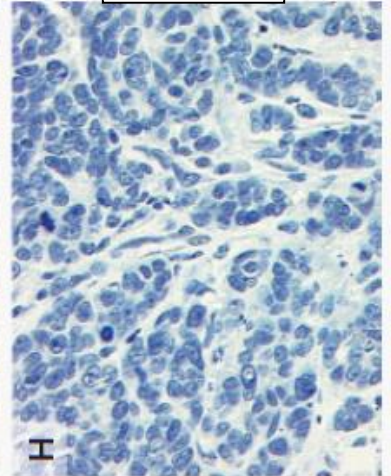
MSH2



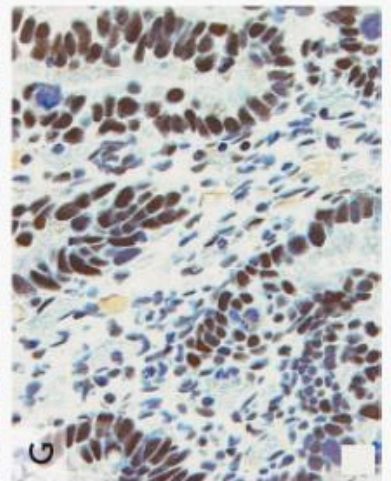
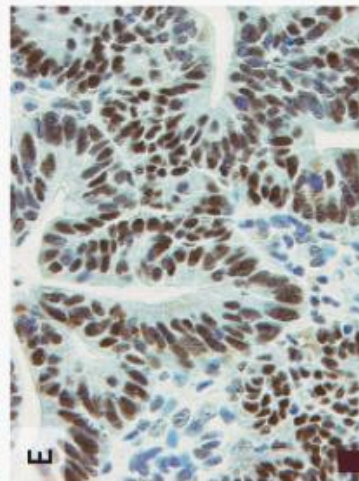
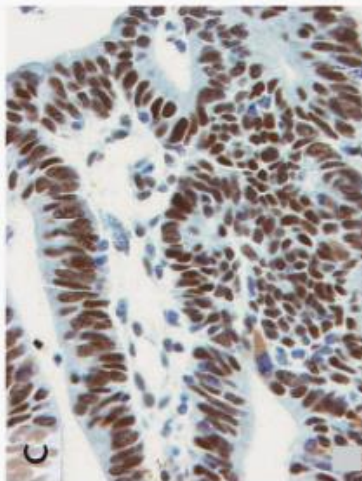
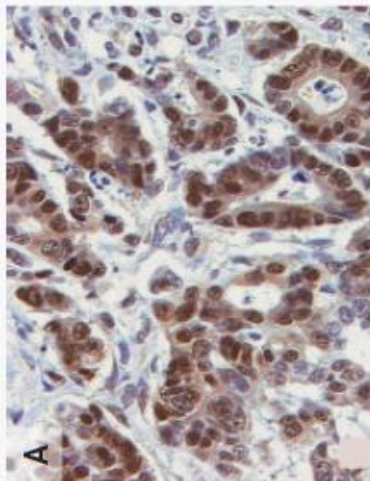
MSH6



PMS2



Normal
IHC



Diagnosis of Lynch syndrome

- Personal and family history
 - Types of cancer
 - Ages of diagnosis
- Testing of tumour
 - MSI testing
 - MMR immunohistochemistry (IHC)
- Genetic testing

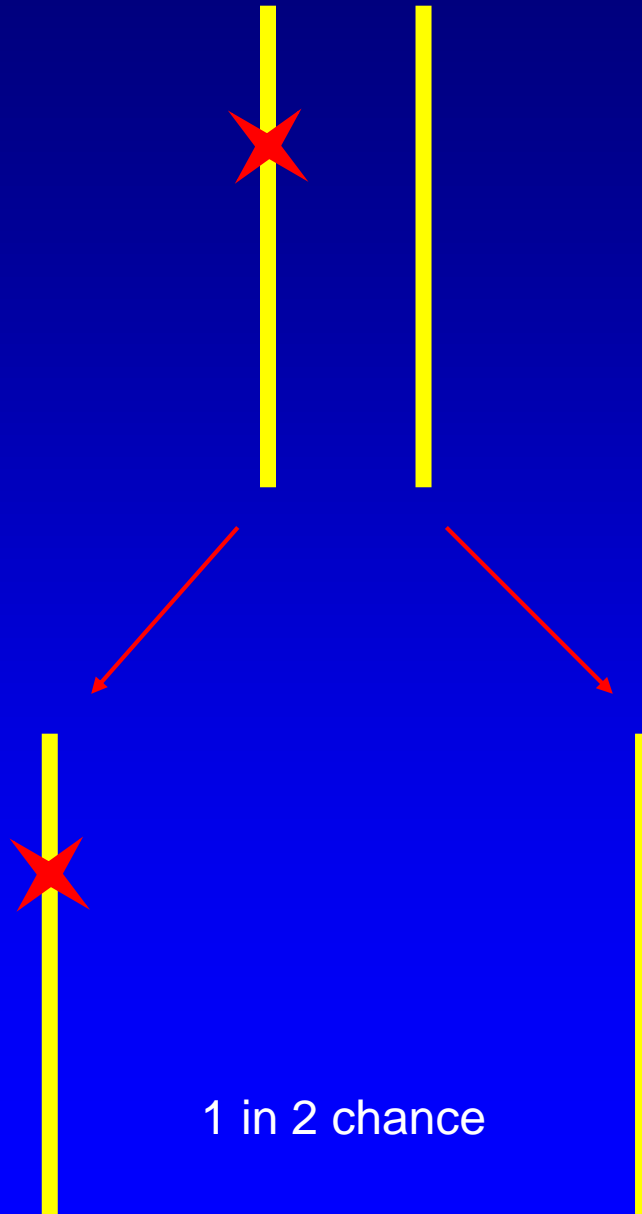
Autosomal Dominant inheritance

Parent

Mismatch repair
gene mutation

Son or daughter

1 in 2 chance



Genetic Testing

- Diagnostic (person has had cancer)
 - Trying to find the gene mutation
- Predictive (person has not had cancer)
 - Someone in family has mutation, know what mutation to look for
 - Yes/No answer
- Preimplantation diagnosis

Features of Lynch CRC

- Accelerated carcinogenesis
- Small adenomas → carcinomas more quickly
 - Younger average age of onset
- Predilection for right sided CRC (but left sided colon cancers do occur)
- Pathology
- Increased risk of a second primary CRC (25-30%)

Cancer risks

Cancer	MLH1 to age 70 yrs 1,2	MSH2 to age 70 yrs 1,2	MSH6 to age 70 yrs 3,2	PMS2 to age 70 yrs 4	Lynch syndrome to age 70 yrs*	General population to age 85 yrs
Colorectal (male)	34%	47%	22%	20%	38%	10%**
Colorectal (female)	36%	37%	10%	15%	31%	6.6%**
Endometrial	18%	30%	25%	15%	33%	2 - 3%
Gastric	6%	0.2%	0	-	6%	1%
Ovarian	8-15%	8-15%	Low	-	9%	1 - 2%
Urothelial	0.2%	2.2%	0.7%	-	<3%	1%
Small Bowel	0.4%	1.1%	0	-	<3%	0.01%

Gene specific effects

- *MLH1* and *MSH2* higher incidence of and earlier onset of colorectal cancer
- Therefore evidence supports later starting age for colonoscopy in *MSH6* and *PMS2* mutation carriers
- *MSH2* higher incidence of extracolonic cancer
- *MSH2* and *MSH6* higher incidence of endometrial cancer

Evidence based risk management of Lynch syndrome

- CRC:
 - Colonoscopy: annual (remove polyps before cancer develops)
- Endometrial and ovarian:
 - Surgery (after childbearing)
- Gastric:
 - Gastrosocopy in families with gastric cancer or high ethnic risk
- www.eviQ.org.au
- Familial Cancer Registry (in all states)

MMR gene mutation frequency in general population

- InSiGHT meeting São Paolo June 2015
 - new data on estimates of the MMR mutation frequency in general population:
 - 1:1900 *MLH1*
 - 1:2800 *MSH2*
 - 1:760 *MSH6*
 - 1:710 *PMS2*
 - **1:280 has an MMR gene mutation**

Awareness

- ~3% of all CRC and endometrial cancer due to Lynch syndrome
- ~17050 CRC and 2050 endometrial cancers will be diagnosed in Australia in 2015
- ~574 Lynch syndrome cases per year

Summary

- Diagnostic methods have changed and improved
- Cancer risks have changed over time as more research undertaken
- Screening works and saves lives
- Education of health professionals is vital
- Research continues.....

Thank you

- Queensland Familial Cancer Registry



The Queensland Familial Cancer Registry (QFCR)

Jan Wakeling, Rachel Susman

Genetic Health Queensland

12 September 2015 – Living with Lynch Syndrome

The QFCR is a register of people who have been diagnosed with an inherited cancer predisposition syndrome (and live in QLD).



The aim of the QFCR is to:

- reduce the incidence of cancer
- increase the chances of detecting cancer at an early stage

.... In Queensland families with an inherited cancer predisposition syndrome

How do people join the QFCR?

1. Patient with a Lynch syndrome like cancer has diagnostic genetic testing at Genetic Health Queensland (GHQ).

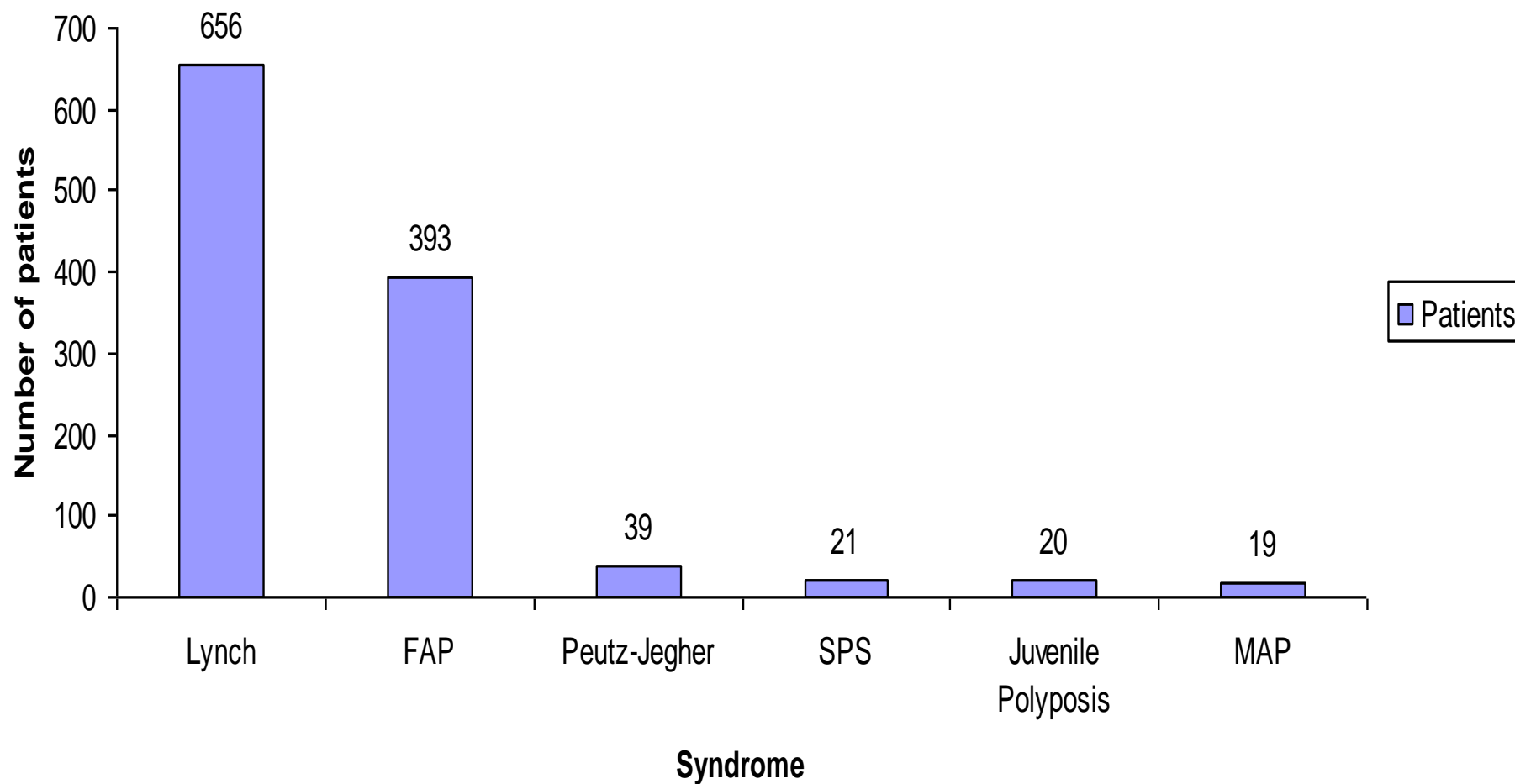
Patient is given a clinical or genetic diagnosis of Lynch syndrome—automatically added to QFCR. (Patients are welcome to opt out)

= Proband

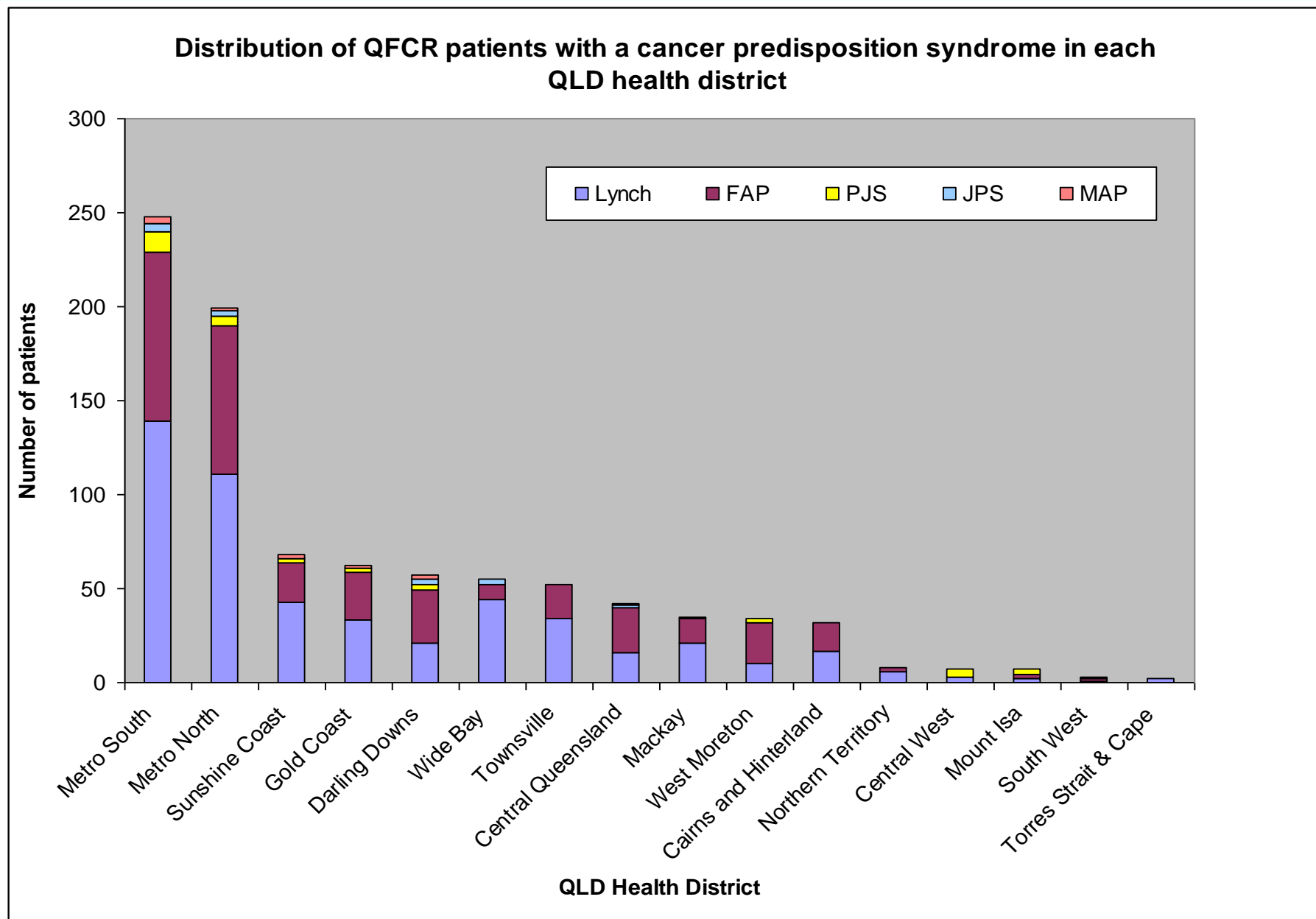
2. Relatives of the proband have predictive genetic testing – those patients with the familial mutation are added to the QFCR.
3. Lynch syndrome patients who were tested interstate or overseas, or privately and referred to GHQ

The Queensland Familial Cancer Registry (QFCR)

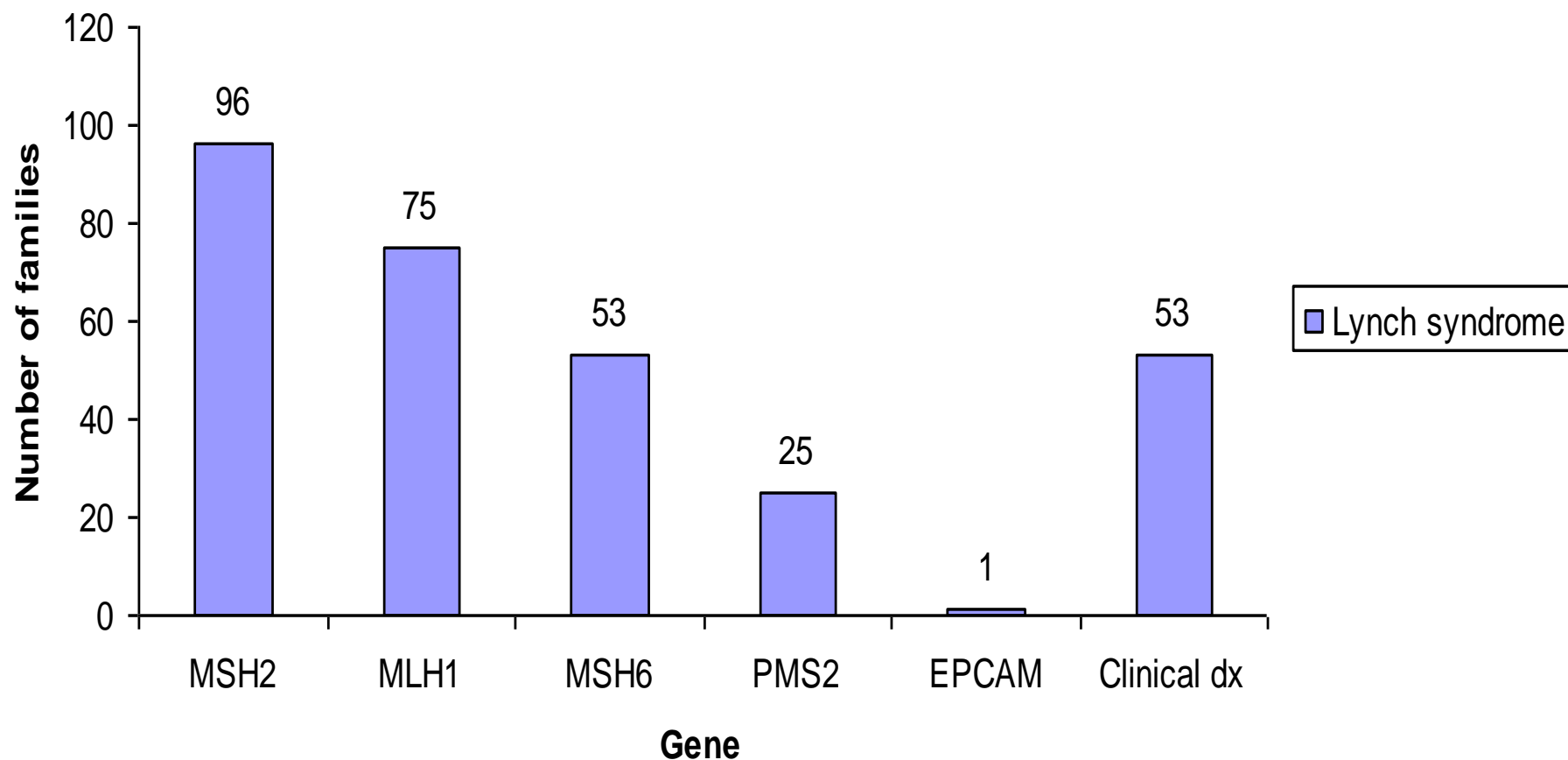
Number of QFCR patients by syndrome
total = 1154, 10 Sept 2015



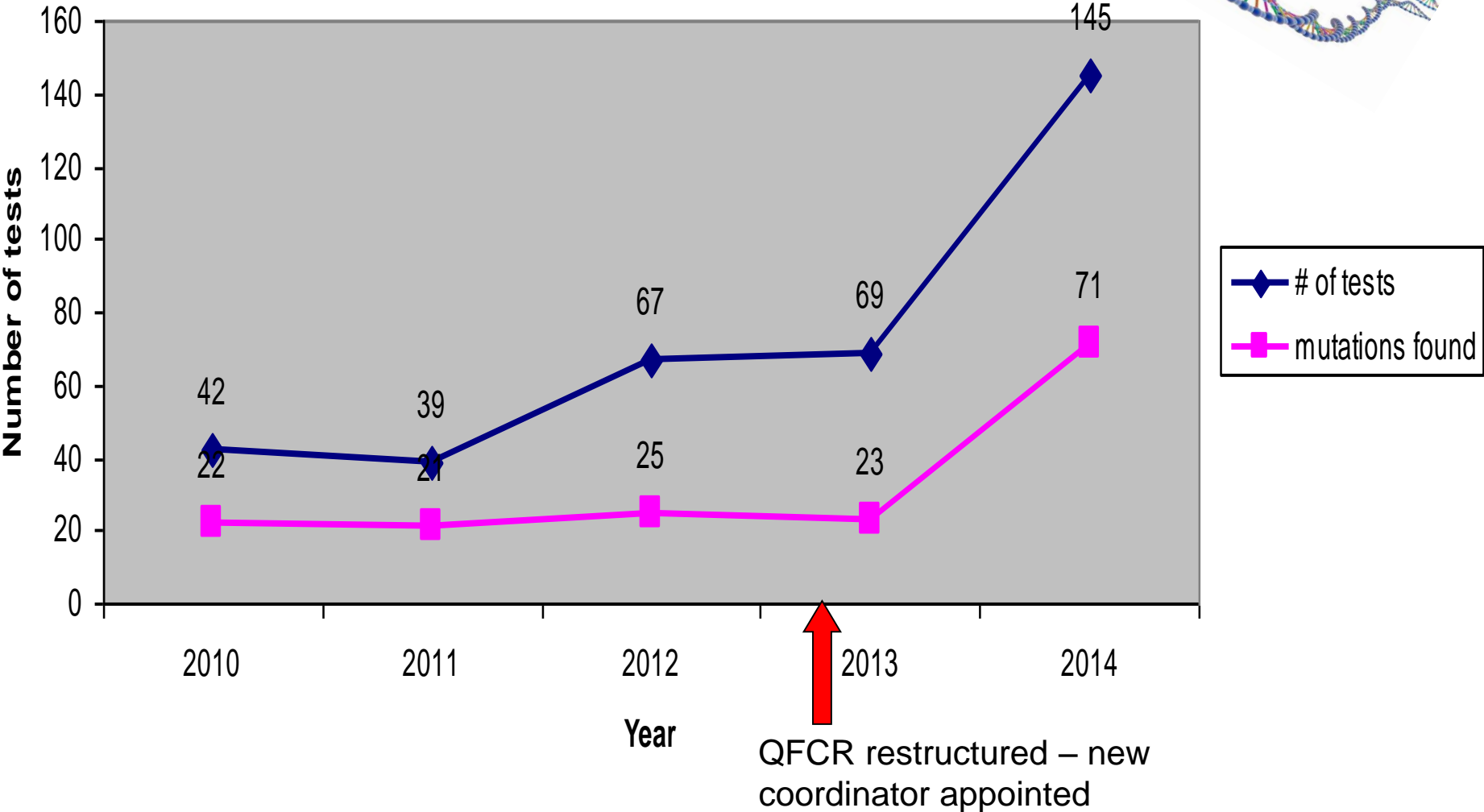
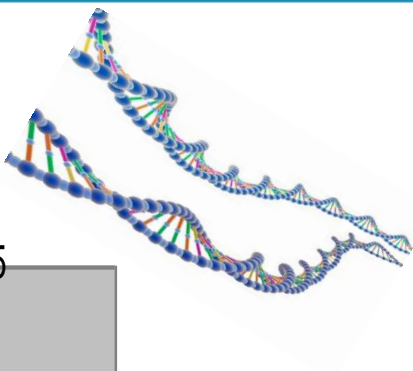
The Queensland Familial Cancer Registry (QFCR)



QLD Families with Lynch syndrome Total number of families = 303, 10 Sept. 2015



5 years of Lynch predictive testing at GHQ



The role of the QFCR

Co-ordinator, (me)

- Appointments for predictive testing and some diagnostic testing
- Send out the screening annual reminder and updated risk management recommendations
- Advocate on behalf of patients
- Education and awareness
 - provide advice to referring GP's about managing patients with Lynch syndrome
 - provide information to patients, families and doctors
 - community engagement give talks to health professionals and patients



Thank you

