

Lynch Syndrome – Understanding the genetics Communicating with family

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Outline of presentation

- Review of the genetics of Lynch Syndrome
- Cancer risks for Lynch Syndrome carriers
- Adjusting to genetic information
- Talking to family about being at risk for Lynch Syndrome
- Talking to children
- Reproductive options



Understanding the genetics



GENETICS
This is how it works

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What is a mutation?

- A Change in the DNA
 - In clinical use, often referred to as a “genetic fault”, “spelling mistake”, “variation”
 - We all have thousands of these, which make us all different
 - Some mutations make a lot of difference to the function of a gene, some don’t change anything
- The “bad cat” analogy

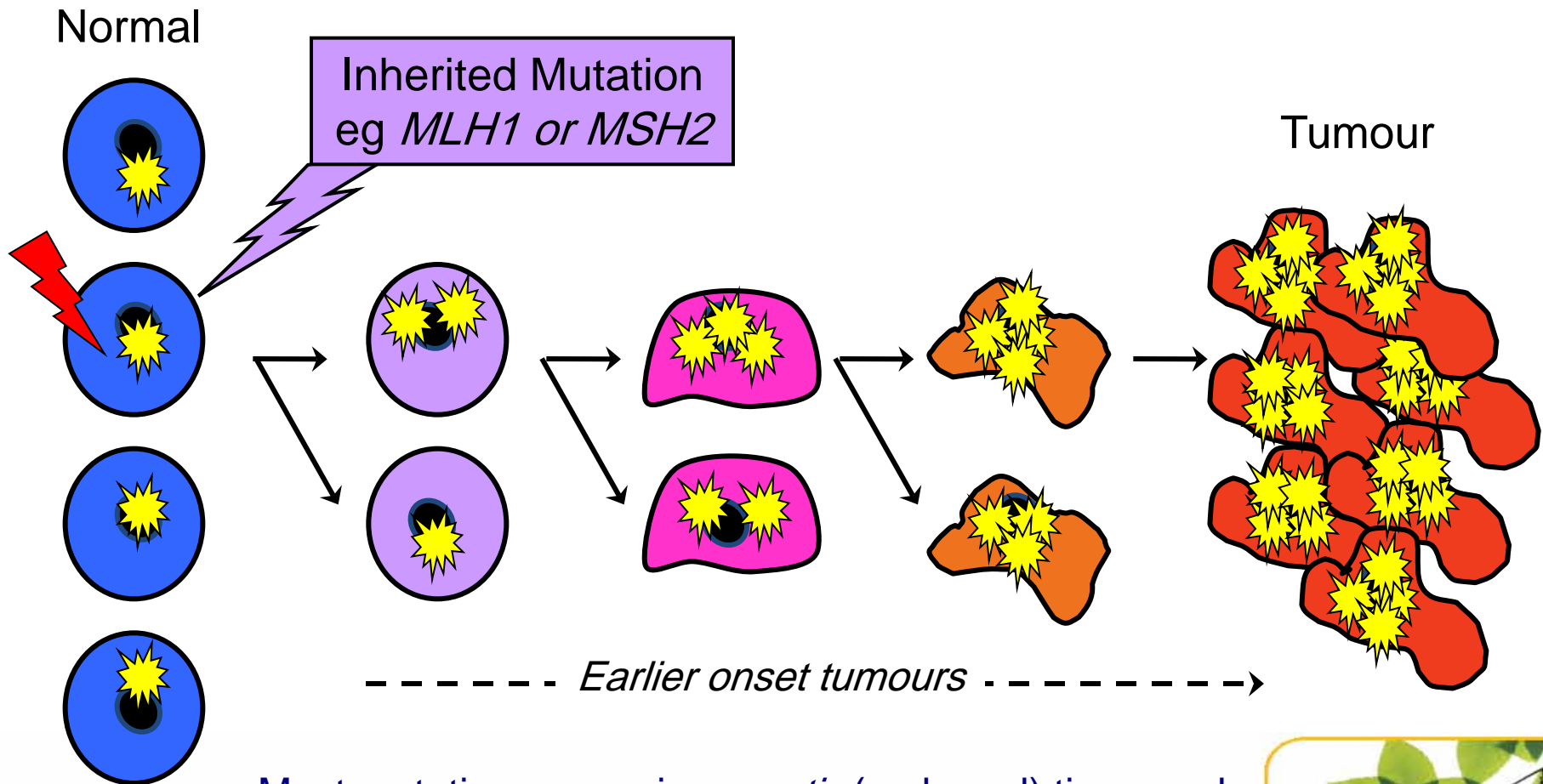


Changes to the DNA code

- Normal DNA code
 - THE BAD CAT SAW THE BIG DOG AND RAN AND BIT HIM
- Single DNA change
 - THE BAD CA^R SAW THE BIG DOG AND RAN AND BIT HIM
 - THE BAD CA^Q SAW THE BIG DOG AND RAN AND BIT HIM
- Insertion
 - THE BAD CAT SAW THE ^{THE} BIG DOG AND RAN AND BIT HIM
 - THE BAD CA^K TSA WTH EBI GDO GAN DRA NAN DBI THI M
- Deletion
 - THE BAD CAT SAW THE _DOG AND RAN AND BIT HIM
 - THE BAD _GAN DRA NDB ITH IM



How can these mutations cause an increased risk of cancer



- Most mutations occur in *somatic* (eg bowel) tissue only
- These gene alterations *cannot be inherited*
- Germline mutation – tumours mainly arise in bowel or other tissue
- These gene alterations *ARE inherited*

Lynch-associated cancer risks by age 70 (95% CI)

	Colorectal cancer	Endometrial cancer	Ovarian cancer	Gastric cancer	Urinary tract cancer	Reference
MLH1	35% (25-50%)	18% (9-34%)	10% (5-25%)	20% men (10-35%)	<3% (0.1-13%)	Dowty et al. 2013 [Barrow et al.2008; Barrow et al. 2009]
				7.5% women (2-20%)		
MSH2	47% men (36-60%)	30% (18-45%)	10% (5-20%)	<10% (1-20%)	10% (3-23%)	Dowty et al. 2013 [Bonadona et al. 2011]
	37% women (27-50%)					
EPCAM (MSH2 silencing)	75%* (65-85%)	12% (0-27%) Higher if near MSH2 promoter	*ascertainment bias – quote MSH2 figures for CRC risk			Kempers et al. 2011
MSH6	22% men (14-32%)	26% (18-36%)	10% other Lynch cancers (1-20%) (includes: ovarian, gastric, small intestine, kidney, ureter, brain)			Baglietto et al. 2009 [Bonadona et al.2011]
	10% women (5-17%)					
PMS2	20% men (11-34%)	15% (6-35%)				Senter et al. (2008)
	15% women (8-26%)					
	25-30% risk of any Lynch cancers					

Why do genetic testing anyway?

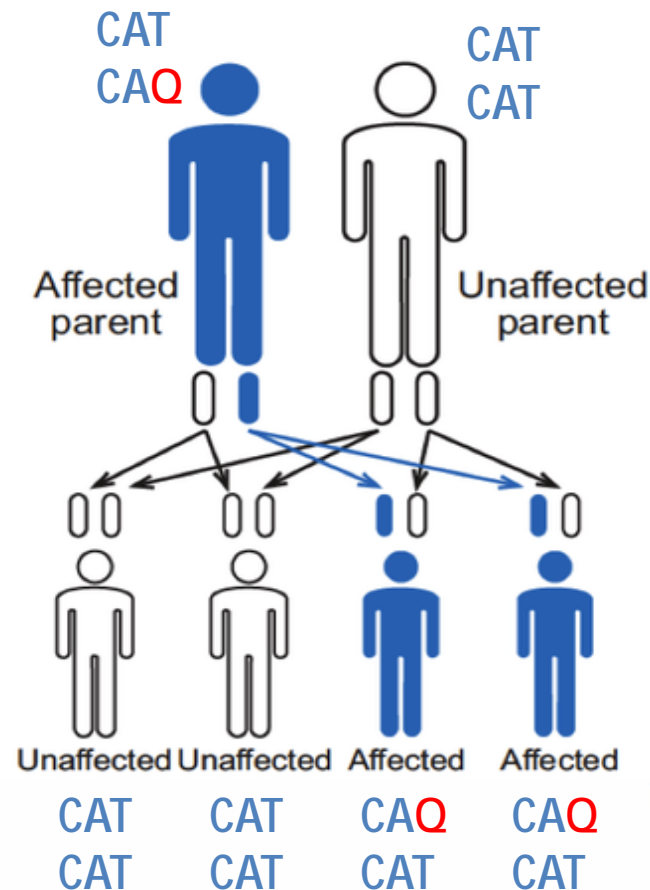
- To determine whether a mutation is present
 - Called “mutation detection”
 - Provides information about future cancer risks
 - Provides information for family members about their risks
 - Can sometimes influence treatment/management
- If a mutation is found
 - Can allow “targeted” genetic testing in family members
 - Called “predictive testing”
 - THE BAD CAQ SAW THE BIG DOG AND RAN AND BIT HIM



How Lynch Syndrome mutations are inherited

- Dominant inheritance

- Inheriting the mutation does not mean you will get cancer, but means the risks are higher
- There are ways to manage the risk
 - Eg colonoscopies
 - surgery

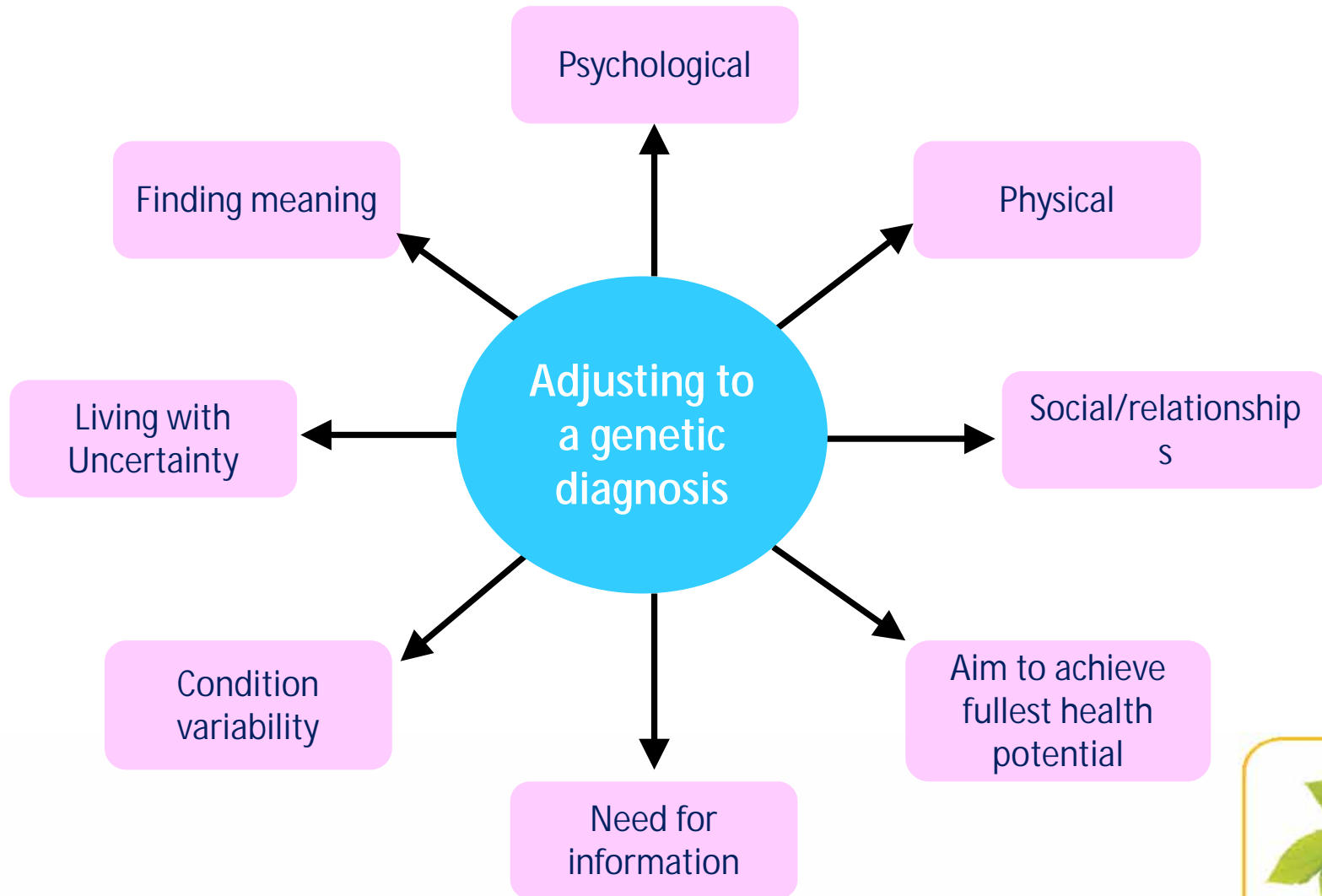


Having Lynch Syndrome - Some of the important issues for families

- Adjustment to genetic information
- Family dynamics and functioning
- Living with uncertainty
- Guilt
- Genetic testing and young people
- Family planning options



“Self” adjustment to a Lynch Syndrome diagnosis



Why is the family important

- **How has your diagnosis of Lynch Syndrome impacted the rest of your family?**
 - Social
 - General health
 - Emergencies
- **How has another family member's experience with Lynch Syndrome impacted how you perceive the disease?**
 - Has it been very difficult or easily manageable
- **How is it treated in your family?**
 - Mentioned a lot or not talked about much
 - Just 'getting on with life' or 'always present'
- **Do specific family members have particular roles in relation to Lynch Syndrome?**
 - The 'check-up' person
 - The person who distances themselves



Family Systems

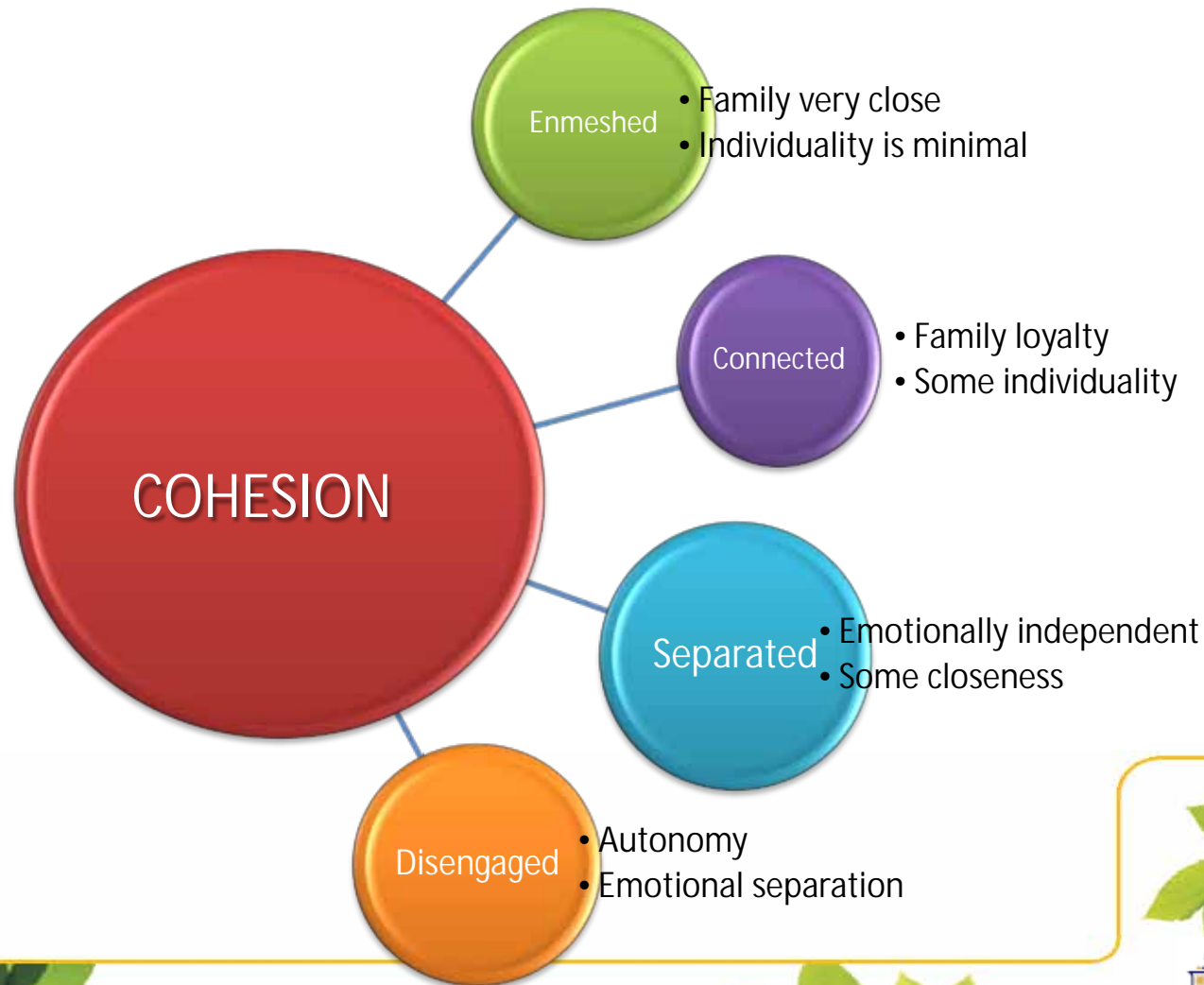


The degree of emotional closeness between family members

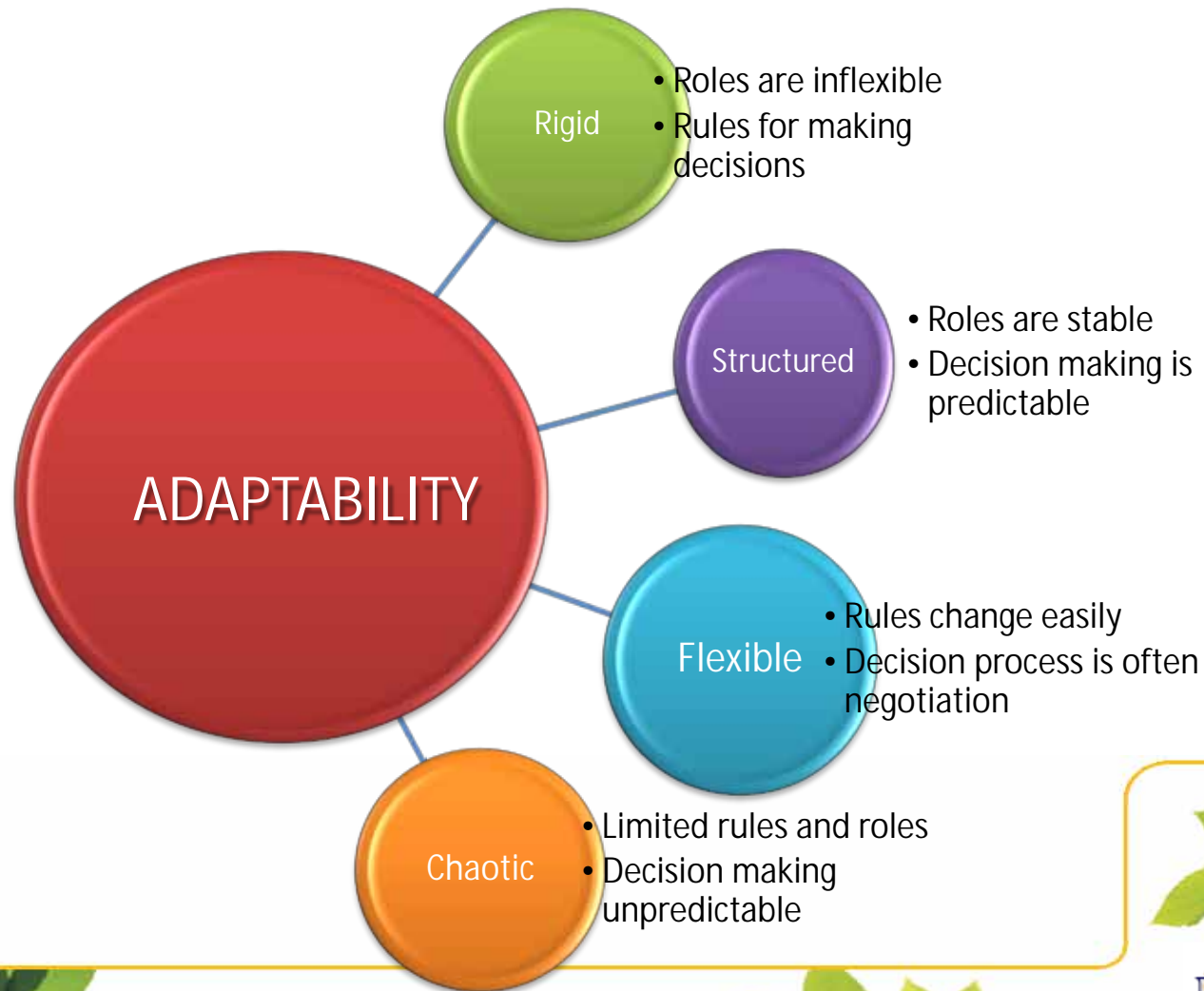
The extent to which a family is flexible in responding to stress and change.

Olson, D. H., and Gorall, D. M., (2003). Circumplex model of marital and family systems. In: Walsh, F (Ed.). *Normal Family Processes* (pp 514-547). New York: Guildford Press.

Theory about family functioning



Theory about family functioning



Where does your family fit?

Thinking of your family through the “lens” of Family Systems theory can help work out how you might cope with Lynch Syndrome in your family



Six-step strategy for communicating genetic information

- Identify relatives/ when / setting
- How much do they know?
- How much do they want to know?
- Share information
- Acknowledge reactions / responses
- Planning



Daly M, et al. Communicating Genetic Test Results to the Family: A Six-Step, Skills-Building Strategy. Family and Community Health; Oct 2001; 24, 3.

Issues for young people

- What is it about young people that is different to adults?
“Adolescence is a time when self-identity is being formulated, peer relations are shifting, and intimate relationships are often first engaged in.”¹
- HOW does genetic testing for Lynch Syndrome impact this?



¹ Rice, F., & Dolgin, K., (2005). The adolescent in a social context. In: *The adolescent: Development, relationships, and culture*. (pp1-53). Boston: Allyn and Bacon Publishers.

Young people – is predictive testing for Lynch Syndrome appropriate

- Are their medical indications for it?
- Does it interfere with development of new relationships?
- Does it cause physical problems or 'embarrassing' circumstances?
- Is the person supported by their family and friends?
- Does it influence or have a role in the formation of their self-identity?



The strengths of parents

- Parents have expertise in dealing with news that have potentially big impacts
- Parents are already experts on their own child, their personality and character, their likely reactions, and so on.
- BUT because this information is different, strain is often experienced; how to tell? When to tell? If/when to offer actual testing?

Genetic testing of young people +/-

Issue	Argument for	Why	Argument against	Why
1. Autonomy	Promotes development of autonomy in decision making	Allows young people to feel like active participants in their own health	Fails to respect future autonomy in denying the opportunity to not know genetic status	Denies the right of the adolescent to an open future
2. Confidentiality			Confidentiality may be breached as results will usually be also made available to parents	This breach may alter the development of the adolescent's independence
3. Psychosocial harm – anxiety/guilt	Harm may occur by not providing the opportunity for testing	Depression and anguish could occur as a result of continued uncertainty in not knowing result	Harm may occur as a consequence of disclosing genetic status	Parents may not be able to convey accurate information regarding genetic risks to their children, resulting in young people blaming themselves for a bad result
4. Psychological harm - Self concept	Testing results could help the adolescent plan adequately for future	Testing could help the adolescent incorporate the result into their self-identity	Harm may occur as a result of changes in self concept associated with result	A positive result may lead to feeling of unworthiness, disrupting development of relationships
5. Decision making process	Allowing parents to be part of the decision-making process could help the adolescent feel supported	Parents could adjust and help the adolescent plan for the disclosure of the result	May be influenced significantly by parents wishes rather than their own	This may lead to parental anxiety or parental guilt which may affect the adolescent indirectly
6. Parent child relationship			There may be harm to the parent-child relationship	Parents may alter their expectations of the adolescent, and alter opportunities afforded to them
7. Family dynamics	May be positively altered by test results	Testing may facilitate openness in the family, resulting in a healthier family environment	May be negatively altered by test results, especially between siblings	Testing may divide siblings or other family members who previously shared a "bond of risk"
8. Discrimination and stigmatisation	Testing may help inform reproductive decisions and career choices	Testing would allow more opportunity to prepare for and pursue life plans	Employment may be affected as well as the ability to obtain life and other types of insurance	Adolescents are yet to establish their vocations and families, and so there is greater scope for effects of discrimination



Guideline

Title

Pre-symptomatic and Predictive Testing for Children and Young Adults

Document Number

2013PS03

Publication Date

August 2014

Replaces

Pre-symptomatic and Predictive Testing for Children and Young Adults 2008PS02

Review Date

2017

Conditions for which there is no medical benefit in the immediate future

The HGSA recommends that pre-symptomatic and predictive testing for *adult onset conditions* should not be undertaken for young people who lack the maturity to appreciate the implications of the test and thus are unable to provide informed consent, either at their own request or at the request of parents/guardians, where:

- There are no treatment(s) that are proven to alter the natural history of the condition and knowledge of genetic status provides no medical benefit in the immediate future, such as Huntington disease (HD) and autosomal dominant spinocerebellar ataxia; or
- Potential medical benefits do not occur until adulthood, such as hereditary breast/ovarian cancer and Lynch syndrome.

The HGSA does not recommend a specific age to differentiate between those whose request for testing should be supported, and those whose request should be declined or deferred. Rather, each request requires individual assessment. In this circumstance, the cognitive and psychosocial maturity of the young person is a crucial consideration with regard to the young person's ability to make an informed decision (see Sections 3, 4). Potential benefits of a mutation negative result need to be considered alongside the perceived benefits and potential harms of a mutation positive result, in the knowledge that either outcome is possible and irreversible. The decision to offer testing must also take into account the relevant jurisdictional laws which enable or prohibit a minor to consent to their own medical management.



It's complicated

- If testing is performed in a young person:
 - Young people should actively be part of the genetic decision making process
- They should be informed (within the context of their age and maturity level)

Testing should be performed for their benefit, not their parents benefit

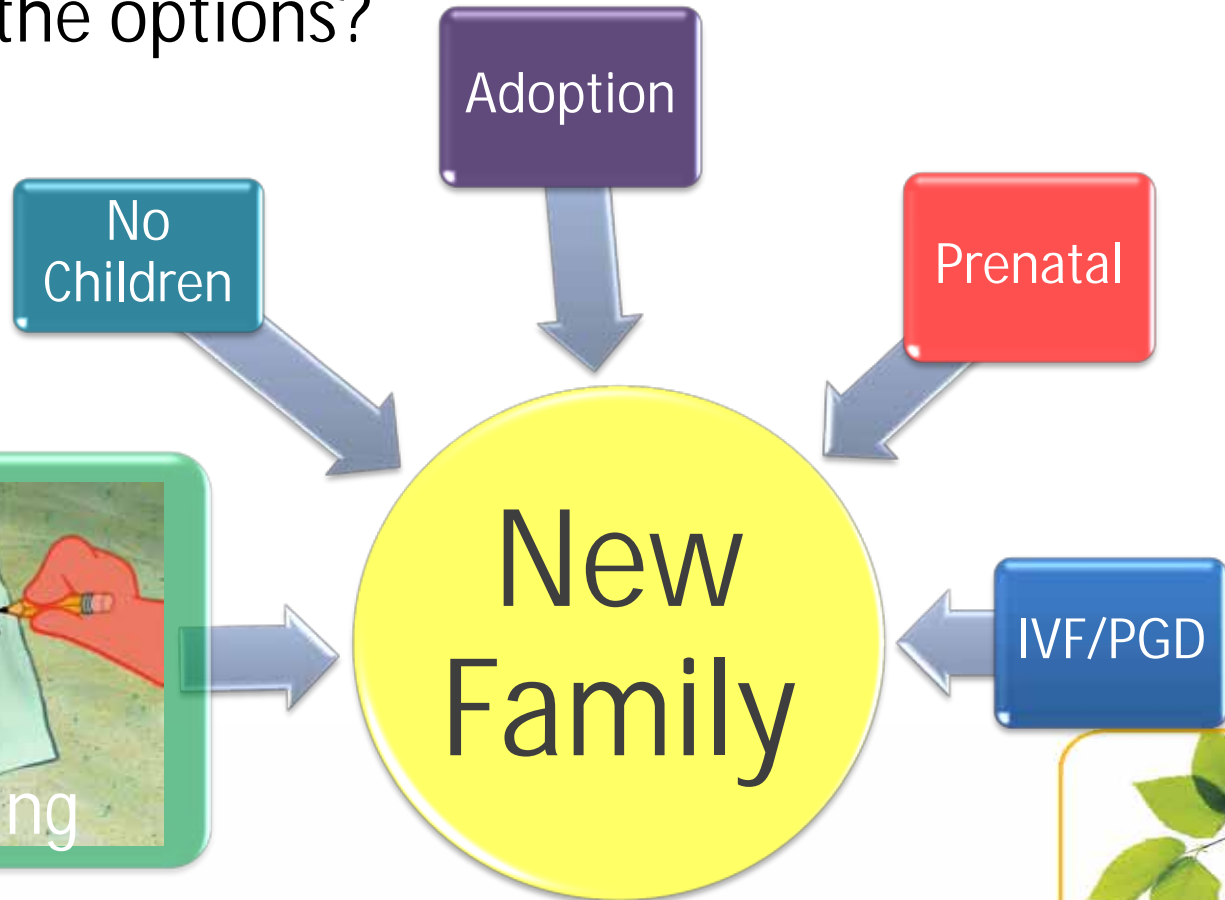


Talking to children

- Having a plan of what/how to talk about the genetic fault in the family avoids being caught off guard
 - Being open and honest with children helps them cope
 - Sharing information will help children not feel excluded
 - Children and young adults comprehend different levels of information
 - Less formal discussions where doing other things alongside their parents
 - Tell story about the condition and how learned to cope with its effects
- Having accurate (not necessarily detailed) information avoids having to go back and change your story (which may convey the message that there is something still scarier awaiting to be discovered)
- Avoiding questions or withholding answers may give the message “You can’t handle this, it’s too scary!”. Don’t be afraid to say-that’s a good question lets talk about that when Dad’s here , the baby’s asleep, things are quieter
- Parents tell their kids lots of bad news and do it well most times
- Support from health professional

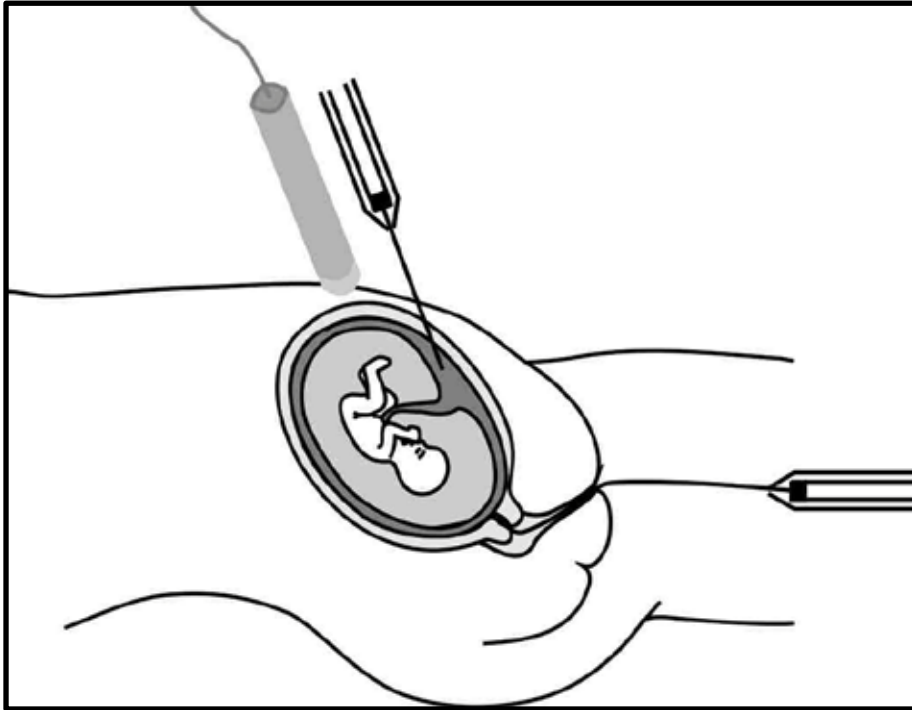
Family planning and Lynch Syndrome

- What are the options?



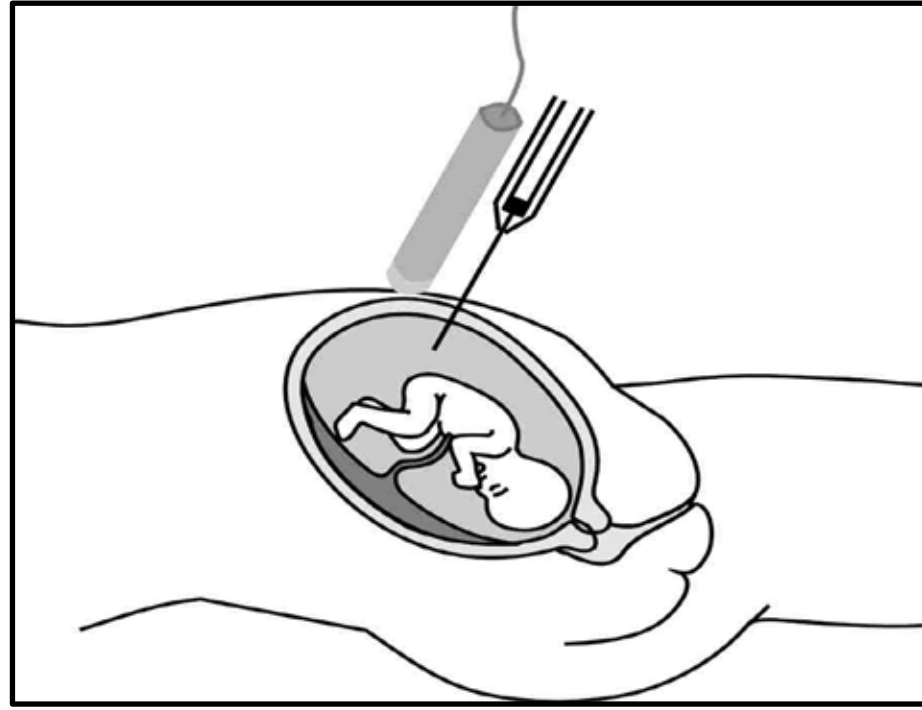
Prenatal testing options

CVS



1:100 or 1% risk of miscarriage
Done between 11-13

Amniocentesis



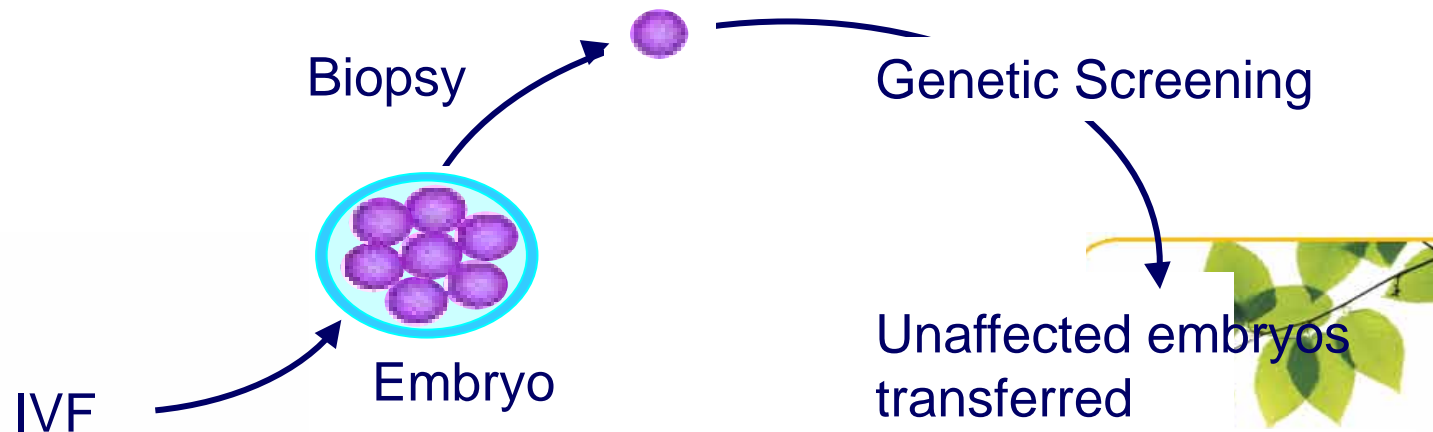
1:200 or 0.5% risk of miscarriage
Done from 15⁺³

Both tests give a definitive answer about Lynch Syndrome genetic status
and other chromosomal conditions (eg Down syndrome)



Assisted Reproductive Technology

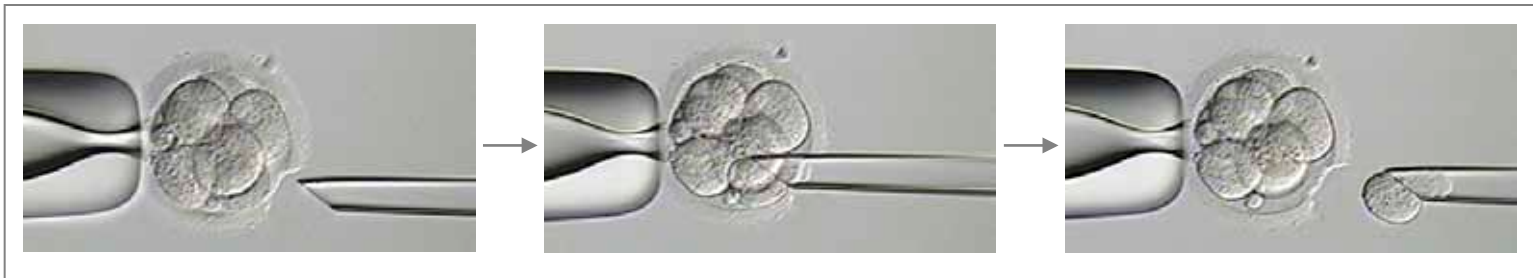
- **Assisted reproductive technology (ART)** is a general term referring to methods used to achieve pregnancy by artificial or partially artificial means.
 - It is used primarily in infertility treatments.
 - Used in fertile couples for genetic reasons. eg. PGD
- Preimplantation genetic diagnosis (PGD) is the process of screening an embryo for genetic or chromosomal conditions prior to implantation



Embryo biopsy & PGD

- Embryo biopsy can be performed at two different time points:

- Day 3 biopsy (removal of 1 or 2 cells)



- Day 5/6 biopsy (removal of ~5 -8 cells)



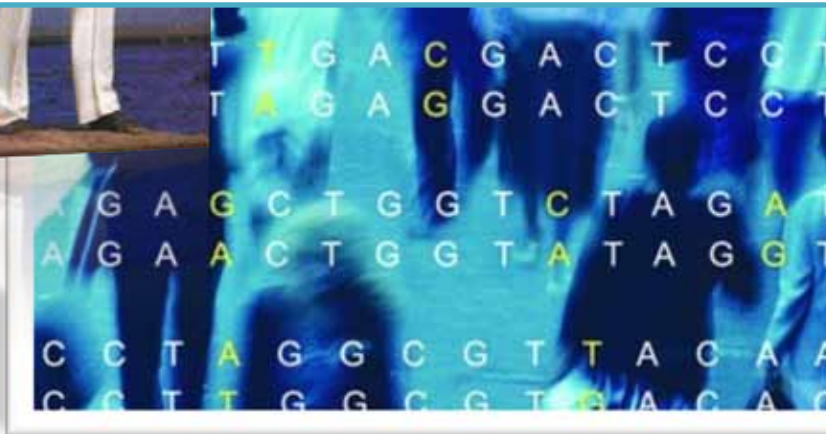
Limitations of PGD

- Couples must undergo an IVF cycle despite the fact that many of these couples are naturally fertile
 - emotionally and physically demanding
- Expensive
- Patient may not stimulate (no eggs)
- Eggs may not fertilise
- Embryos may not be suitable for biopsy
- A result may not be obtained for all embryos... then what?
- Embryos may not be suitable for transfer
- Transferred embryo/s may not implant
- Not a 100% guarantee of result
- No guarantee that the couple will get pregnant
 - ~40-55% pregnancy rate



Normalisation

We are all different



Family Cancer Centres (FCCs)

- Locations
 - Royal Melbourne Hospital
 - Monash Medical Centre
 - Peter MacCallum Cancer Centre
 - Austin Health
 - Regional clinics are serviced by the FCCs
 - (eg RMH: Geelong, Western Health, Warrnambool)
- Victorian Family Cancer Genetics Service, contact the Cancer Helpline 13 11 20

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