Genetic Research in Human Populations

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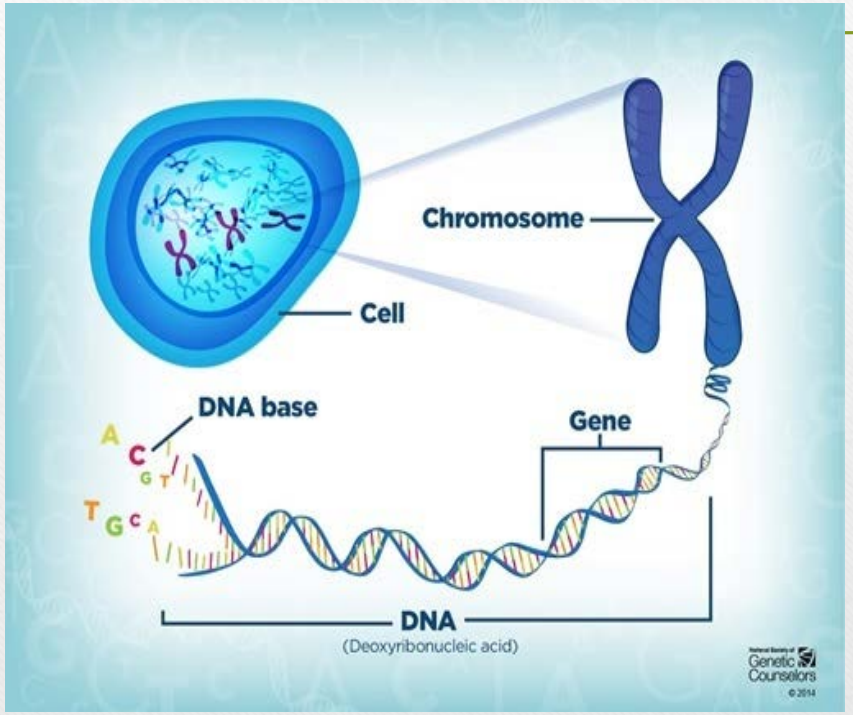
Learning objective

- Introduction
- Common examples of genetics research
- Ethical Issues
- Legal and regulatory issues
- Store and Use of biological samples
- Consent
- Case study

Genetics Research



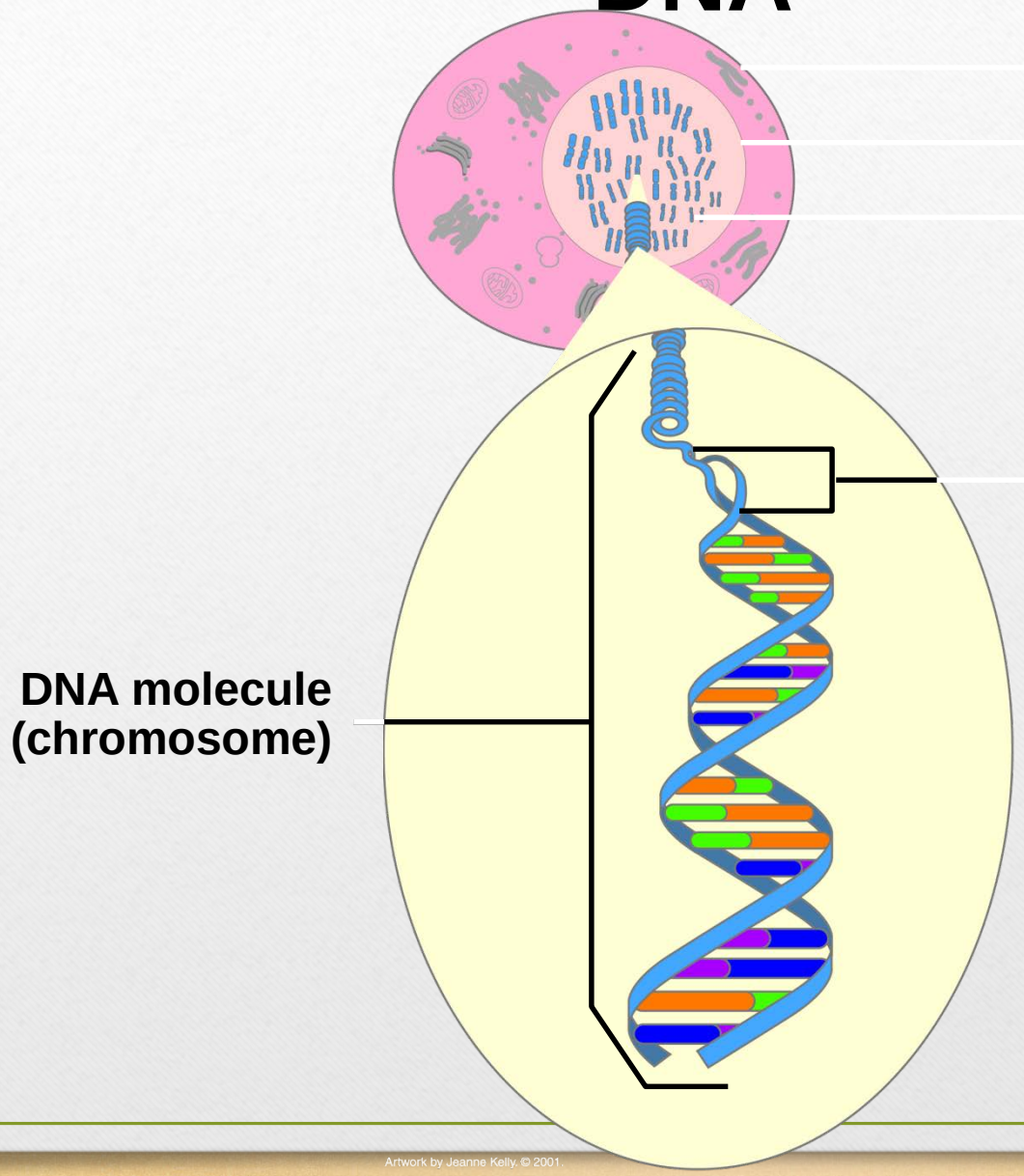
- Genetic test
- Genome sequencing research
- Chromosome

Understanding Gene Testing

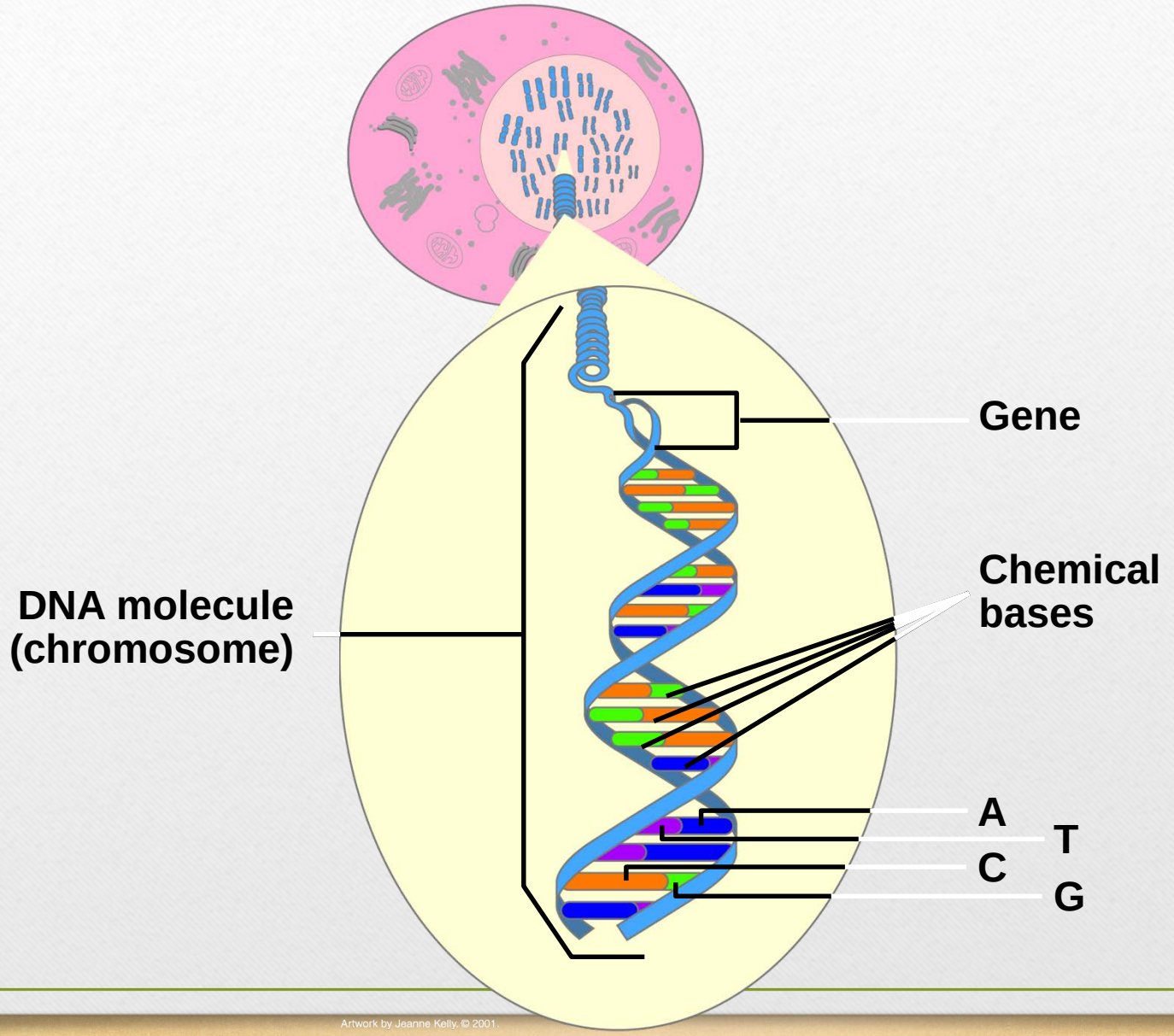
Developed by:
Lydia Schindler
Donna Kerrigan, M.S.
Jeanne Kelly
Brian Hollen

Illustrates what genes are, explains how mutations occur and are identified within genes, and discusses the benefits and limitations of gene testing for cancer and other disorders.

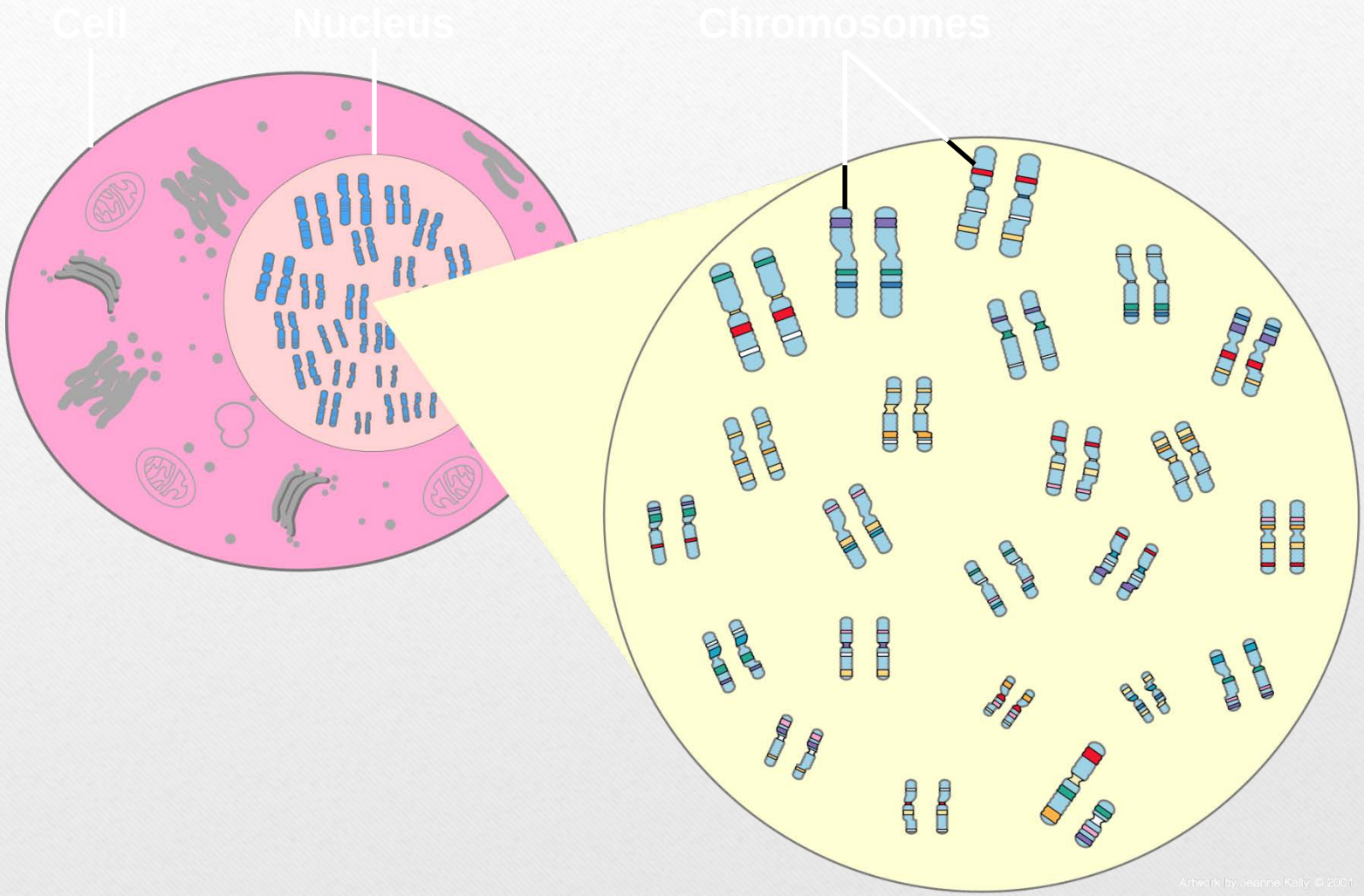
DNA



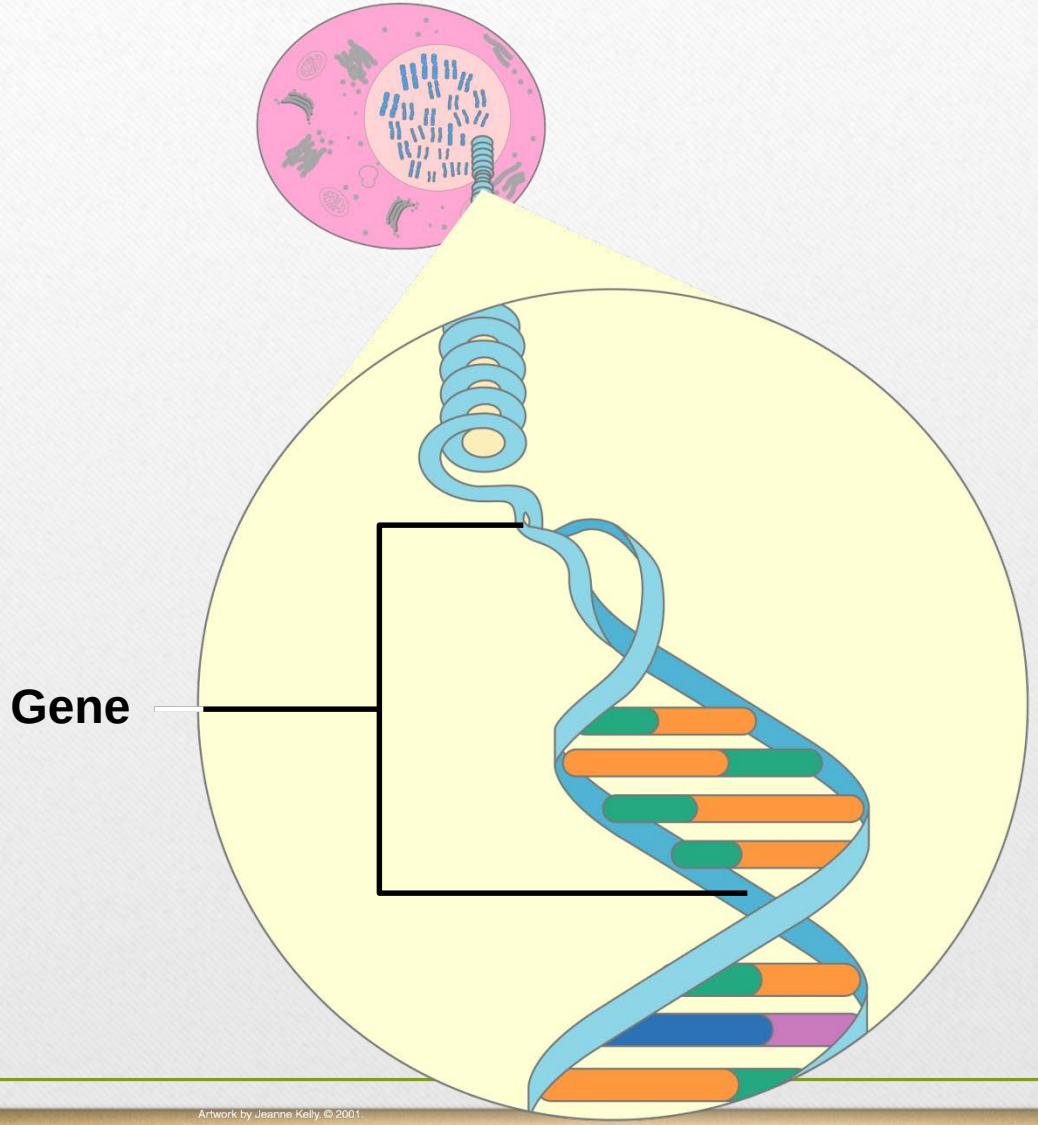
Chemical Bases in DNA



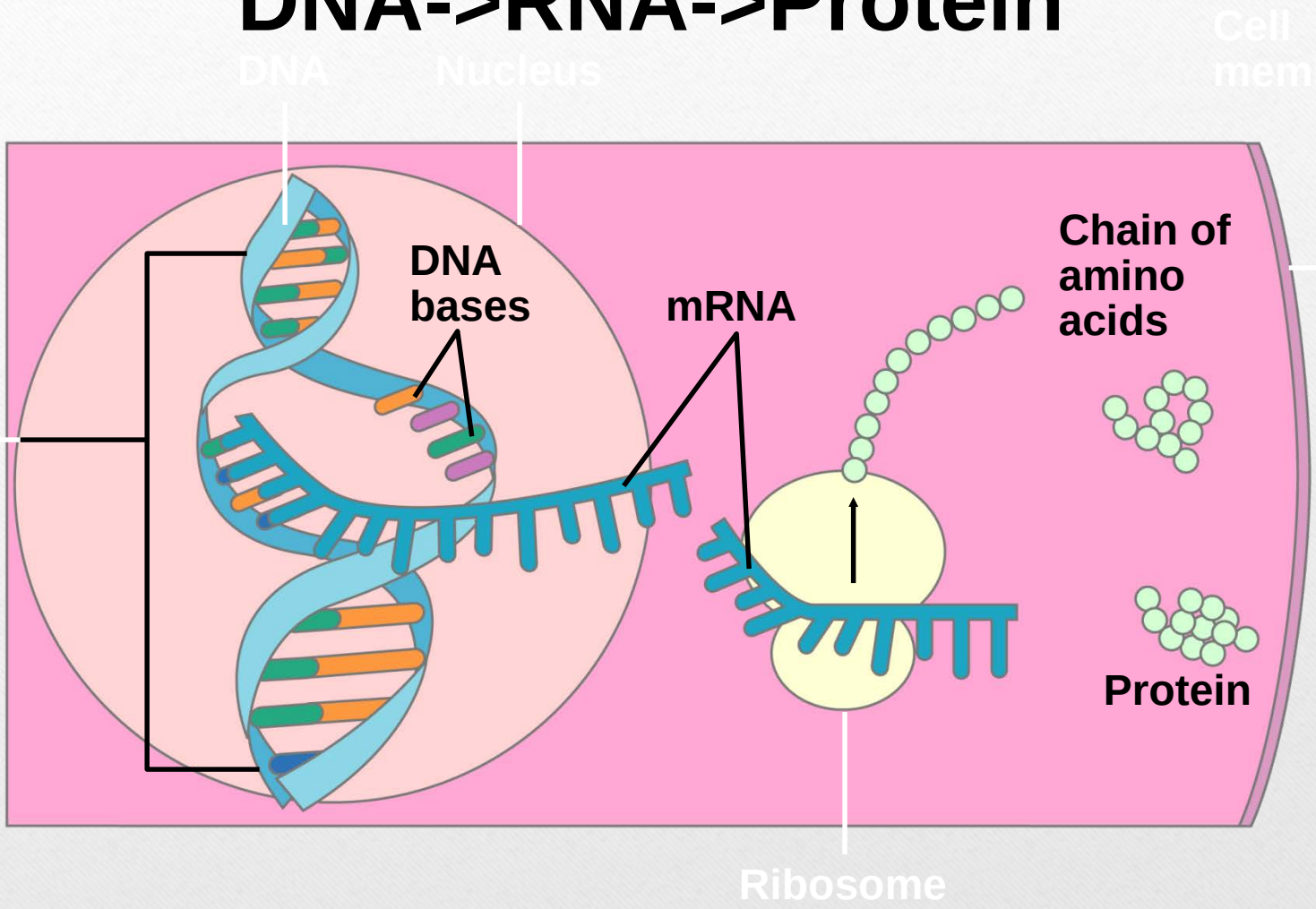
DNA Molecules



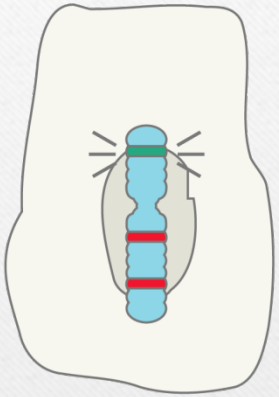
Gene Subunits



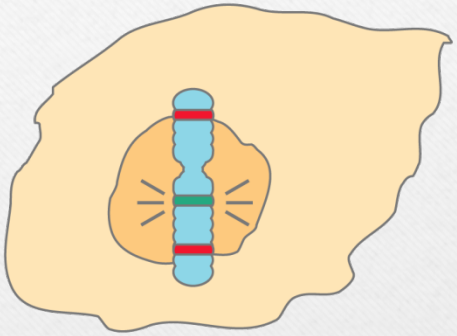
DNA->RNA->Protein



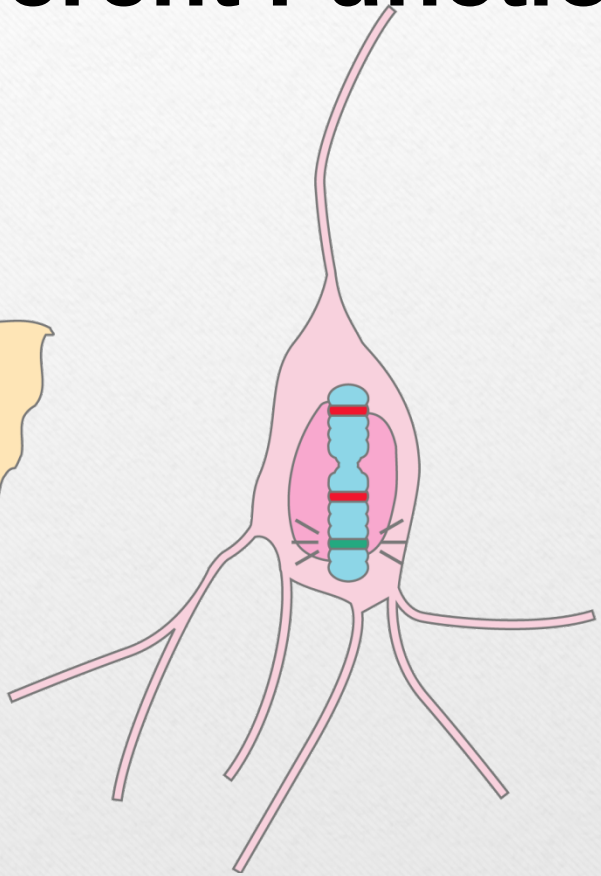
Different Genes – Different Functions



Bone Cell

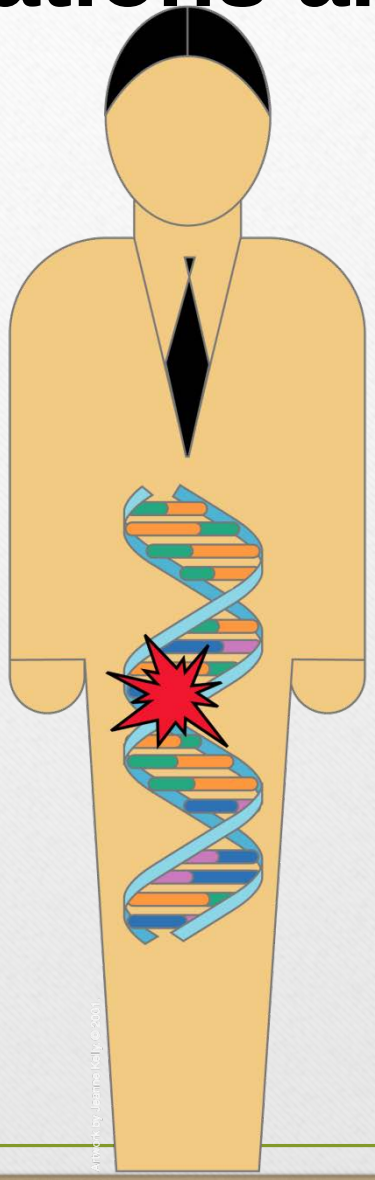


Pancreas Cell



Brain Cell

Gene Mutations and Disease



Genetic Test

- Test to make diagnosis in a person who has features of a genetic disorder
- Test to determine the presence or absence of a genetic variant, or variants, in a person who has no features of the disorder at the time of testing, in order to use the information to predict the likelihood that person will develop the disorder in the future

Diagnostic test

- Make diagnosis
- Provide appropriate management
- Genetic counseling to the affected person
- Advise family members

Presymptomatic test

- A test performed on a person who has no symptoms of a specific disorder at the time of testing, to determine whether or not he/she has a mutant gene
- Identify the specific mutation present in the family
- If the mutant gene is shown to be present, the person is almost certain to develop symptoms of the disorder at some time in the future

Predictive test

- A test performed on a person who has no symptoms of a specific disorder at the time of testing, to determine whether or not he/she has a mutant gene
- If the mutant gene is present
- The person has a high probability to developing symptoms of the disorder

Susceptibility test

- A test performed on person who has no symptoms of a specific disorder at the time of the test
- To determine whether or not she/he has a genetic variant or variants which increase the likelihood that the person will develop symptoms of the disorder (the risk increase are often small)

Carrier test

- mutated gene or chromosome abnormality which will not effect the person's health,
- increases his/her chance of having children with the disorder in question. (autosomal recessive, X-linked recessive , a balanced chromosome rearrangements)

Screening test

- A screening test is one that is performed on individuals not known to be at increased risk of a particular disorder
- no family history
- No symptom or other reason to suggest an increased risk.

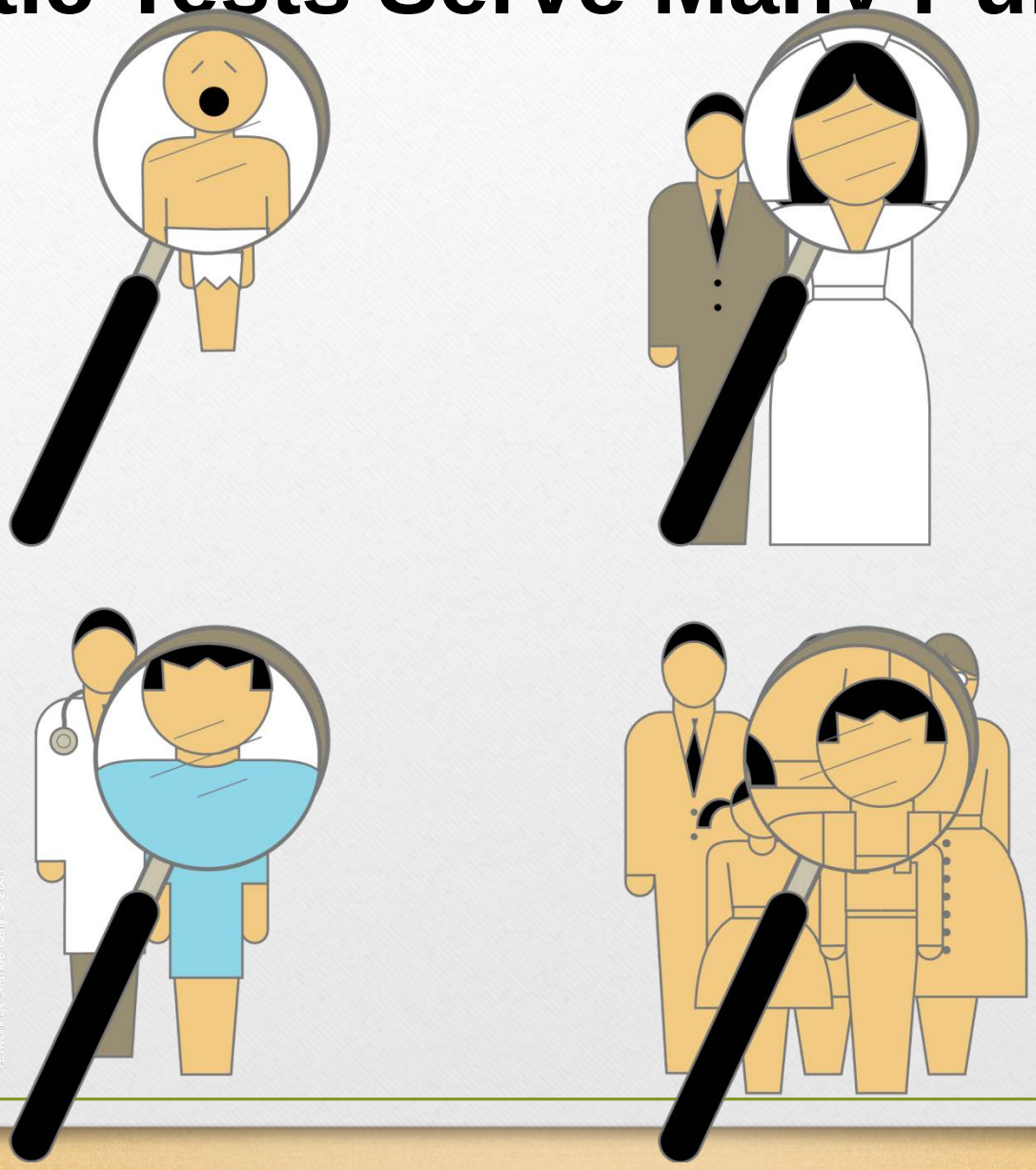
Prenatal test

- **A test , usually diagnosis or presymtomatic, carried out on a developing fetus.**

Preimplantation test

- A form of presymptomatic test carried out on early embryos in the laboratory, with a view to transferring to the mother's uterus only those which will not develop the disorder in question.

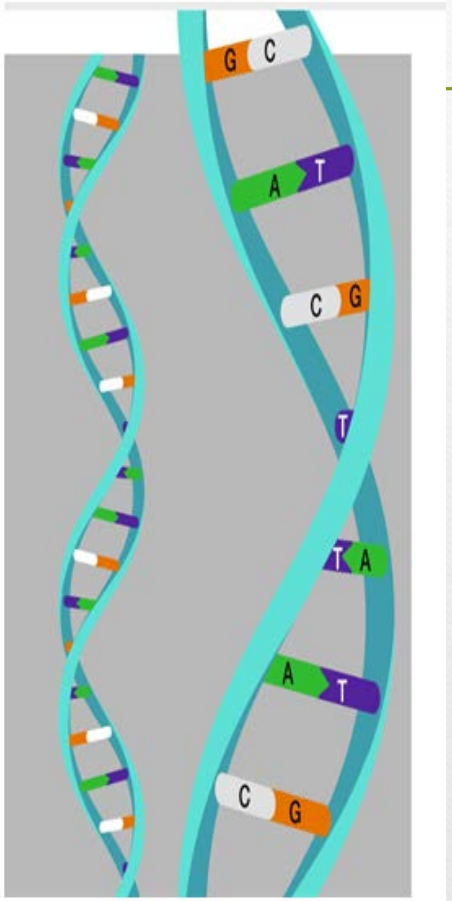
Genetic Tests Serve Many Purposes



What's a genome?

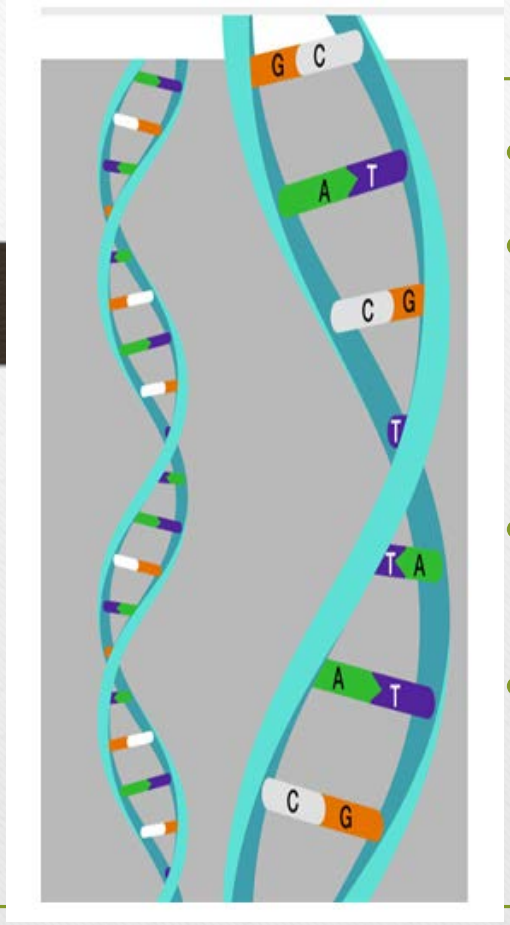
- A living organism have their own Genome
- Genome is a fancy word for all your DNA
- Each genome contain the information needed to build and maintain that's organism throughout it's life
- Your genome is the operating manual containing all the instructions that helped you develop from a single cell into the person you are today. It guides your growth, helps your organs to do their jobs, and repairs itself when it becomes damaged. And it's unique to you. The more you know about your genome and how it works, the more you'll understand your own health and make informed health decisions.

The DNA Double Helix



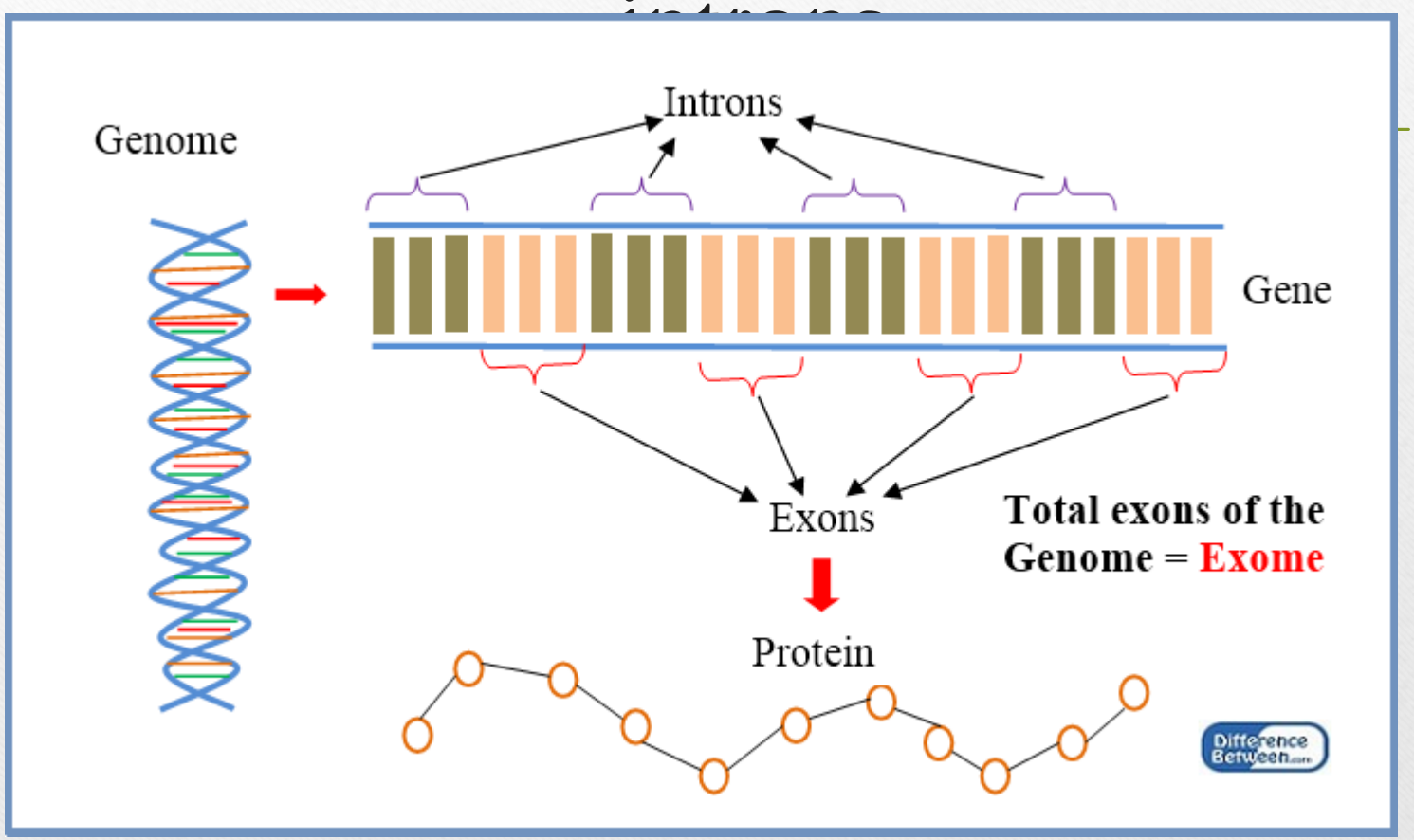
- Genome are made of DNA, and extreme large molecule that look like the long twisted ladder
- **Double helix is the description of the structure of a DNA molecule.**
- Attached to each sugar is one of four **bases: adenine (A), cytosine (C), guanine (G), or thymine (T).**

The DNA Double Helix



- DNA is read like a code.
- This code is made up of 4 types of chemical building block, adenine, thymine, cytosine and guanine abbreviated with the letter A T C and G.
- The order of the letters in this code allows the DNA to function in different ways
- The code changes slightly from person to person to help make you who you are.

Genes are composed of exons, introns



Genome Sequencing

- **Whole genome sequencing (WGS)**

  Sequencing of all all human genome

- **Whole exome sequencing (WES)**

  Sequencing of all protein-coding regions in the human genome (the exome) , only 2% 0f sequencing and exome harbor about 85% 0f mutation with large effects on disease related traits

Ethical considerations

- Recruitment of research subjects
- Researcher-Clinician (Successful research outcome than with the patient care)
- Method to approach Family members both affected and non affected to be enrolled in the study

Ethical considerations

- Confidentiality, privacy and security
- Disclosure information to other family members should be include in the initial process of consent
- Family members information should be store in the way that cannot be request to get the information by simply request from the medical record.

Consent to Genetic testing

- Consent (informed ,voluntary and competent)
- Genetic counseling Relevant information, possible consequences of the available choices, providing practical help with decision making, providing emotional support

Aim of the consent

- Enable the person considering testing to make a decision with the best possible outcome
- Provided information
- Free and informed choice
- Avoid directive way
- No deliberate deception or coercion

Information

- What are the types of genetic testing?
- How is the genetic testing done?
- What do the results of genetic tests mean?
- What are the benefit of the genetic testing?
- What are the risks and limitations of the genetic testing?
- What is the costs and turnaround time?

Requirement of the common rule

(elements that are important to genetic research)

- A statement about the whether the research project might include whole genome sequencing
- A statement that biospecimens may be used for commercial profit and whether the subject will or will not share in this commercial profit
- A statement about whether clinically relevant research results will be disclose to the subject

Vulnerable Groups
(Special concern)

- Ethnic specific subjects
- Children
- Disability
- Pregnant women
- Fetus , embryo

Potential benefits

- Benefit to human health
- Susceptibility to disease, and precautions that can be taken to prevent disease
- Knowledge about risk of having a child with a genetic condition and a strategies to avoid (adoption, prenatal testing or preimplantation genetic diagnosis)

Potential harm

- **Discrimination**
- **Social stigmatization**
- **Person future relationship.**
- **Harmful implications for individuals as a member of community or ethnic group such as study for genetic cause of disability, ethnicity and disease, behaviour.**

Psychological benefit for predictive genetic testing

- Minimizes the possibility of serious psychological maladjustment later in life induced by late discovery status
- Decreased parental and child anxiety
- Decreased uncertainty about the future
- More realistic life choices
- Elimination of risk
- More openness about genetic conditions within family and society in general

Some potential harm

- Development of a perception that a person is “ill”
- Low self esteem on the part of the person tested
- Serious psychological maladjustment, even perhaps depression and suicide
- Parental guilt

Some potential harm

- Social discrimination , including future employment and insurance discrimination
- May remove child's autonomy to make decisions as an adult
- Change in family perceptions and expectations for child
- Identification of other family members at risk who wish not to know.

Privacy and Confidentiality

- Diagnostic test for symptomatic individual, the information in the medical record and will be available for those who would have access
- Individual privacy and confidentiality
- Presymptomatic and predictive test information should be placed in the medical record ,only the test has been done and how to request the test result.
- Some Predictive information will be the basis of implementing preventive intervention

Individual privacy and the family

- Genetic information provide information about the individual as well as the individual ‘s family
- The relative of the case of Familial adenomatous polyposis are at risk to developing this disorder which almost always results in bowel cancer.
- Preventive measures are available to those who inherited the disorder

Individual privacy and the family

- Generally accepted that an individual has responsibilities to the family as well as a right to the privacy and confidentiality.
- Balance carefully about the right to privacy and disclosure genetic information could lead to the avoidance of a substantial chance of harm to a relative

Blood relative

- The fact that a genetic test may provide information of a significance to other family members should be discuss prior to testing, if appropriate
- Consent for a blood relative to access genetic information or material which may assist in clarifying the blood relative's susceptibility to a disorder or a chance of having affected children

Ethical issues associated with genomic research.

- challenges because they produce fine, detailed, genotype information at high resolution, and the results of more focused studies can potentially be used to determine genetic variation for a wide range of conditions and traits
- The information from a GWA scan is derived from DNA that is a powerful personal identifier, and can provide information not just on the individual, but also on the individual's relatives, related groups, and populations
- creates large amounts of individual-specific digital information that is easy to share across international borders

Special considerations for Genomics Research

- Board versus specific consent
- Consideration for families
- Consideration for identifier populations
- Study involve children
- Study involving participant who cannot give consent
- Data and sample sharing through data repositories and Biobank.
- Return of results and incidental finding to the participants

The American College of Medical Genetics recommendations

- The American College of Medical Genetics and Genomics has published recommendations about reporting incidental findings in the exons of certain genes
- DNA mutations are found in certain genes they should be reported to individuals because of their potential high medical importance.

Broad versus Specific consent

- **The informed consent process should reflex the research use for which samples, genetics data and health information might be shared.**
- **Broad consent in combination or additional with specific consent for some disease –specific research that consider genomic, storage sample and data for future unspecified research.**

Common Rule Specific Issues

Specimen Banking

When is Operating a Human Specimen Bank considered research?

- Activity of creating and maintaining a specimen bank for research purposes to be a research activity

Operationally

- Specimen repositories that either involve interaction or intervention with the subject to obtain the specimens or that that record and maintain identifying information associated with the specimen should develop a protocol for their operations and submit that to IRB for approval

Is the deposit of specimen into a tissue bank considered research?

- If the tissue bank supports research activities, then yes, the collection and placement of those specimens into a bank is considered to be part of research process

OFFICE FOR PROTECTION FROM RESEARCH RISKS

Issues to Consider in the Research Use of Stored Data or Tissues

Tissue Collector

IRB Review
Informed consent
Submittal agreement
Assurance of Compliance

Repository Storage &Data Management Center

IRB Review
Sample of informed consent
Certificate of Confidentiality
Assurance of compliance

Recipient Investigator

Recipient Agreement
Local policy

Human Tissue Repositories

- The collector of tissue samples
- The repository storage and data management center
- The recipient investigators

IRB Review

- Regulatory requirements in each component
- Informed consent
- Submittal agreement
- Sample Informed consent
- Certificate of Confidentiality
- Recipient Agreement
- Local policies

Data and Tissue Storage

Lists of question concerning tissue and data storage for future research:

- **Explicit mention in the consent form of the duration and data storage**
- **How such tissue and data will be used in the future?**
- **Whether such uses will be limited to the studying disease for which the tissue was obtained to begin with.**
- **The issues of whether and how future genetic testing results will be conveyed to study subjects.**

Data and Tissue Storage

Lists of question concerning tissue and data storage for future research:

- **Will tissues samples and data be distributed to investigators outside of the study during the future research ?**
- **Where will tissue and data be stored?**
- **Will tissue and data be discarded at the conclusion of the study?**
- **Will tissue and data be retained for future research, including Genetic testing?**

Data and Tissue Storage

Lists of question concerning tissue and data storage for future research:

- **Will there be secondary distribution of tissue and/or data and how will subjects' confidentiality be protected?**
- **How will the results of the future genetic testing be handled with respect to person**
- **When withdrawing from participation in a study can subjects request that sample be destroyed or anonymized or require that the data does not be used**

Types of samples

- Anonymous : No personal identifiers
- Anonymized : Personal identifiers removed completely
- Coded : Linked to personal identifiers
- Identified : Personal identifiers attached

Legal and regulatory issues

พระราชบัญญัติ คุ้มครองข้อมูลส่วนบุคคล พ.ศ. ๒๕๖๒

พระราชบัญญัติ

คุ้มครองข้อมูลส่วนบุคคล

พ.ศ. ๒๕๖๒

พระบาทสมเด็จพระปรเมนทรรามาธิบดีศรีสินทรมหาวชิราลงกรณ
พระวชิรเกล้าเจ้าอยู่หัว

ให้ไว้ ณ วันที่ ๒๔ พฤษภาคม พ.ศ. ๒๕๖๒
เป็นปีที่ ๔ ในรัชกาลปัจจุบัน

สาระสำคัญของ พ.ร.บ.ฉบับนี้มี 3 ประเด็นดังนี้

- 1. เจ้าของข้อมูลต้องให้ความยินยอมในการเก็บรวบรวม การใช้ และการเปิดเผยข้อมูลส่วนบุคคลตามวัตถุประสงค์ที่ผู้เก็บรวบรวม ผู้ใช้ แจ้งไว้ตั้งแต่แรกแล้วเท่านั้น
- 2. ผู้เก็บรวบรวมข้อมูลต้องรักษาความมั่นคงปลอดภัยของข้อมูล ไม่ให้มีการเปลี่ยนแปลงแก้ไข หรือถูกเข้าถึงโดยผู้ที่ไม่เกี่ยวข้องกับข้อมูล เช่น สถานพยาบาลจะต้องเก็บข้อมูลของผู้ป่วยให้เป็นความลับและไม่เปิดเผยให้กับผู้อื่น
- 3. เจ้าของข้อมูลมีสิทธิ์ถอนความยินยอม ขอให้ลบหรือทำลายข้อมูลเมื่อใดก็ได้

ข้อมูลชีวภาพ

- ข้อมูลส่วนบุคคลที่เกิดจากการใช้เทคนิคหรือเทคโนโลยี ที่เกี่ยวข้องกับการนำลักษณะเด่นทางกายภาพหรือทางพฤติกรรมของบุคคลมาใช้
- ทำให้สามารถยืนยันตัวตน ของบุคคลนั้นที่ไม่เหมือนกับบุคคลอื่นได้
- เช่น ข้อมูลภาพจำลองใบหน้า ข้อมูลจำลองม่านตา หรือข้อมูลจำลองลายนิ้วมือ
- Whole genome sequencing

Consent Template by FERCIT

- Informed consent form for clinical trials
- Broad informed consent form for storage and use of data
- Informed consent form for genetic research

Guideline and Template of Informed Consent Form for Clinical Trials in Thailand

หนังสือแนวทาง และต้นแบบ
เอกสารข้อมูล และขอความยินยอม สำหรับการวิจัยทางคลินิกในประเทศไทย

หากสนใจกรุณาติดต่อ **คุณอรศิริ 02-3543981**หรือ dmu_pcm@hotmail.com
ราคาขายเล่มละ 200 บาท ราคาสมาชิก 120 บาท

UPDATE!! Download template ได้ที่นี่.

	Template	Checklist
1. Informed consent form for clinical trials	1_FERCIT ICF template_clinical trials_ver1.0 [Word] [PDF]	1_ICF checklist_clinical trials_ver1.0 [Word] [PDF]
2. Broad informed consent form for storage and use of data and biospecimens for future research	2_FERCIT ICF template_broad consent_ver1.0 [Word] [PDF]	2_ICF checklist_broad consent_ver1.0 [Word] [PDF]
3. Informed consent form for genetic research	3_FERCIT ICF template_genetic research_ver1.0 [Word] [PDF]	3_ICF checklist_genetic research_ver1.0 [Word] [PDF]

แหล่งที่มา : ณัฐ คูณรังษีสมบูรณ์, ทิพาพร ธาระวานิช, ขัยรัตน์ ฉายากุล. แนวทางและต้นแบบเอกสารข้อมูลและขอความยินยอมสำหรับการวิจัยทางคลินิกในประเทศไทย (Guidance and template of informed consent form for clinical trials in Thailand). กรุงเทพ: สำนักพิมพ์จุฬาลงกรณ์มหาวิทยาลัย, 2563. (โดยได้รับอนุญาต)

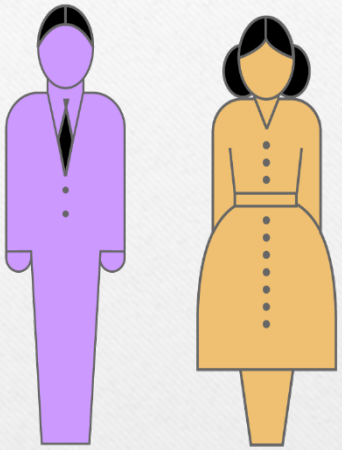
Case study

Huntington Disease

Huntington disease

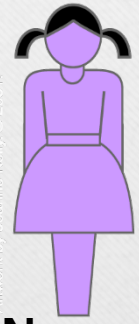
- neurological degenerative disease
- onset in the most people between the ages of 35 and 60 (approx.)
- no cure for this disorder which is slowly progressive over around 10 years and
- involves a deterioration in movement, cognition and generalized functioning.
- Death usually results from respiratory illness.

Huntington Disease Dominant Genes

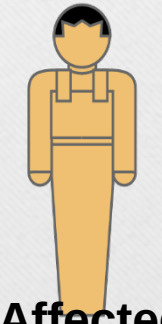


Normal Father

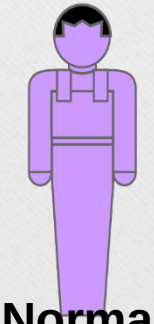
Affect Mother



Normal Daughter



Affected Son



Normal Son

Affected Daughter

Predictive Genetic Testing in Children

- **Mrs Smith 38 years old and has recently diagnosed as carrying the gene for Huntington's disease, she will develop progressive and irreversible dementia and movement disorder between the age of 40-60.**
- **Mrs Smith has 16 years old son (John) and 11 years old daughter (Jane)**

Parental autonomy

- Mrs Smith would like to have a tested for Hungtinton's on her children
- She want John to know the result of the test (old enough to know)
- Does not want Jane know the result

Mrs Smith's opinion

- Competent child
- Better Psychosocial adjustment
- Knowledge about themselves
- If she know, she carrying the gene, she would have children sooner or would not work so hard and spent more time with them

Doctor's opinion

- Predictive testing fails to respect child's later autonomy ; right not to know
- Professional guidelines; advise against genetic testing in children when you can't do anything to prevent or treat the disease.
- Can cause harm to the child: depress, stop them from challenging career, some people committed suicide

What is your opinion?

Predictive Genetic Testing in Children

- Predictive Genetic testing should only be performed on children if it is in their best interest. ”interest” include psychosocial elements.
- Predictive testing is performed on children when there are interventions to prevent disease or to detect and treat it early and it is necessary to begin these interventions in childhood. It is also performed for disease known to commence in childhood

Predictive Genetic Testing in Children

- Predictive testing in children for adult-onset conditions for which there is no medical intervention is highly controversial.
- Competent children and adolescents can consent to predictive testing

Predictive Genetic Testing in Children

- Predictive testing can result in harm, such as discrimination (eg, in insurance entitlement or employment) and stigmatisation.
- Predictive testing can have important non-medical benefits in terms of self-knowledge and life planning