

# BIOINFORMATICS

UNIT 3 ( 3.2)

## **Bioinformatics- Introduction and Applications**

- With a large number of prokaryotic and eukaryotic genomes completely sequenced and more forthcoming, access to the genomic information and synthesizing it for the discovery of new knowledge have become central themes of modern biological research.
- Mining the genomic information requires the use of sophisticated computational tools.
- It therefore becomes imperative for the new generation of biologists to initiate and familiarize with a field of study that is concerned with the careful storage, organization and indexing of information in order to tackle the new challenges in the genomic era.
- Information science has been applied to biology to produce a field is called bioinformatics.
- It is concerned with the state of- the-art computational tools available to solve biological research problems.
- The term bioinformatics was coined by Paulien Hogeweg and Ben Hesper to describe “the study of informatic processes in biotic systems” and it found early use when the first biological sequence data began to be shared.
- Bioinformatics is an interdisciplinary field that develops methods and software tools for understanding biological data.
- The development of bioinformatics as a field is the result of advances in both molecular biology and computer science over the past 30-40 years.
- As an interdisciplinary field of science, bioinformatics combines biology, computer science, information engineering, mathematics and statistics to analyze and interpret biological data.
- The key areas of bioinformatics include biological databases, sequence alignment, gene and promoter prediction, molecular phylogenetics, structural bioinformatics, genomics, and proteomics.

## ***Bioinformatics vs Computational Biology***

- Bioinformatics differs from a related field known as computational biology.
- Bioinformatics is limited to sequence, structural, and functional analysis of genes and genomes and their corresponding products and is often considered computational molecular biology.
- However, computational biology encompasses all biological areas that involve computation.
- Bioinformatics as the development and application of computational tools in managing all kinds of biological data, whereas computational biology is more confined to the theoretical development of algorithms used for bioinformatics.

## ***Applications of Bioinformatics***

*Bioinformatics has not only become essential for basic genomic and molecular biology research, but is having a major impact on many areas of biotechnology and biomedical sciences. The main uses of bioinformatics include:*

- *Bioinformatics plays a vital role in the areas of structural genomics, functional genomics, and nutritional genomics.*
- *It covers emerging scientific research and the exploration of proteomes from the overall level of intracellular protein composition (protein profiles), protein structure, protein-protein interaction, and unique activity patterns (e.g. post-translational modifications).*
- *Bioinformatics is used for transcriptome analysis where mRNA expression levels can be determined.*
- *Bioinformatics is used to identify and structurally modify a natural product, to design a compound with the desired properties and to assess its therapeutic effects, theoretically.*
- *Cheminformatics analysis includes analyses such as similarity searching, clustering, QSAR modeling, virtual screening, etc.*
- *Bioinformatics is playing an increasingly important role in almost all aspects of drug discovery and drug development.*
- *Bioinformatics tools are very effective in prediction, analysis and interpretation of clinical and preclinical findings.*

## ***Applications in Other Fields***

*Its major applications include in the following fields:*

### ***Molecular medicine***

- *The human genome will have profound effects on the fields of biomedical research and clinical medicine.*
- *The completion of the human genome and the use of bioinformatic tools means that we can search for the genes directly associated with different diseases and begin to understand the molecular basis of these diseases more clearly.*
- *This new knowledge of the molecular mechanisms of disease will enable better treatments, cures and even preventative tests to be developed.*

### ***Personalised medicine***

- *Clinical medicine will become more personalised with the development of the field of pharmacogenomics.*
- *This is the study of how an individual's genetic inheritance affects the body's response to drugs.*
- *Today, doctors have to use trial and error to find the best drug to treat a particular patient as those with the same clinical symptoms can show a wide range of responses to the same treatment.*
- *In the future, doctors will be able to analyse a patient's genetic profile and prescribe the best available drug therapy and dosage from the beginning.*

### **Preventative medicine**

- With the specific details of the genetic mechanisms of diseases being unravelled, the development of diagnostic tests to measure a persons susceptibility to different diseases may become a distinct reality.

### **Gene therapy**

- In the not too distant future with the use of bioinformatics tool, the potential for using genes themselves to treat disease may become a reality.
- Gene therapy is the approach used to treat, cure or even prevent disease by changing the expression of a person's genes.

### **Drug development**

- At present all drugs on the market target only about 500 proteins.
- With an improved understanding of disease mechanisms and using computational tools to identify and validate new drug targets, more specific medicines that act on the cause, not merely the symptoms, of the disease can be developed.
- These highly specific drugs promise to have fewer side effects than many of today's medicines.

### **Microbial genome applications**

- The arrival of the complete genome sequences and their potential to provide a greater insight into the microbial world and its capacities could have broad and far reaching implications for environment, health, energy and industrial applications.
- For these reasons, in 1994, the US Department of Energy (DOE) initiated the MGP (Microbial Genome Project) to sequence genomes of bacteria useful in energy production, environmental cleanup, industrial processing and toxic waste reduction.
- By studying the genetic material of these organisms, scientists can begin to understand these microbes at a very fundamental level and isolate the genes that give them their unique abilities to survive under extreme conditions.

### **Waste cleanup**

- *Deinococcus radiodurans* is known as the world's toughest bacteria and it is the most radiation resistant organism known.
- Scientists are interested in this organism because of its potential usefulness in cleaning up waste sites that contain radiation and toxic chemicals.

### **Climate change Studies**

- Increasing levels of carbon dioxide emission, mainly through the expanding use of fossil fuels for energy, are thought to contribute to global climate change.
- Recently, the DOE (Department of Energy, USA) launched a program to decrease atmospheric carbon dioxide levels.
- One method of doing so is to study the genomes of microbes that use carbon dioxide as their sole carbon source.

### **Alternative energy sources**

- Scientists are studying the genome of the microbe *Chlorobiumtepidum* which has an unusual capacity for generating energy from light

### **Biotechnology**

- The archaeon *Archaeoglobusfulgidus* and the bacterium *Thermotogamaritima* have potential for practical applications in industry and government-funded environmental remediation.
- These microorganisms thrive in water temperatures above the boiling point and therefore may provide the DOE, the Department of Defence, and private companies with heat-stable enzymes suitable for use in industrial processes
- Other industrially useful microbes include, *Corynebacteriumglutamicum* which is of high industrial interest as a research object because it is used by the chemical industry for the biotechnological production of the amino acid lysine.
- The substance is employed as a source of protein in animal nutrition.
- Biotechnologically produced lysine is added to feed concentrates as a source of protein, and is an alternative to soybeans or meat and bonemeal.
- *Lactococcuslactis* is one of the most important micro-organisms involved in the dairy industry.
- Researchers anticipate that understanding the physiology and genetic make-up of this bacterium will prove invaluable for food manufacturers as well as the pharmaceutical industry, which is exploring the capacity of *lactis* to serve as a vehicle for delivering drugs.

### **Antibiotic resistance**

- Scientists have been examining the genome of *Enterococcus faecalis*-a leading cause of bacterial infection among hospital patients.
- They have discovered a virulence region made up of a number of antibiotic-resistant genes that may contribute to the bacterium's transformation from a harmless gut bacteria to a menacing invader.
- The discovery of the region, known as a pathogenicity island, could provide useful markers for detecting pathogenic strains and help to establish controls to prevent the spread of infection in wards.

### **Forensic analysis of microbes**

- Scientists used their genomic tools to help distinguish between the strain of *Bacillus anthracis* that was used in the summer of 2001 terrorist attack in Florida with that of closely related anthrax strains.

### **The reality of bioweapon creation**

- Scientists have recently built the virus *poliomyelitis* using entirely artificial means.
- They did this using genomic data available on the Internet and materials from a mail-order chemical supply.

- The research was financed by the US Department of Defence as part of a biowarfare response program to prove to the world the reality of bioweapons.
- The researchers also hope their work will discourage officials from ever relaxing programs of immunisation.
- This project has been met with very mixed feelings.

### ***Evolutionary studies***

- The sequencing of genomes from all three domains of life, eukaryota, bacteria and archaea means that evolutionary studies can be performed in a quest to determine the tree of life and the last universal common ancestor.

### ***Crop improvement***

- Comparative genetics of the plant genomes has shown that the organisation of their genes has remained more conserved over evolutionary time than was previously believed.
- These findings suggest that information obtained from the model crop systems can be used to suggest improvements to other food crops.
- At present the complete genomes of *Arabidopsis thaliana* (water cress) and *Oryza sativa* (rice) are available.

### ***Insect resistance***

- Genes from *Bacillus thuringiensis* that can control a number of serious pests have been successfully transferred to cotton, maize and potatoes.
- This new ability of the plants to resist insect attack means that the amount of insecticides being used can be reduced and hence the nutritional quality of the crops is increased.

### ***Improve nutritional quality***

- Scientists have recently succeeded in transferring genes into rice to increase levels of Vitamin A, iron and other micronutrients.
- This work could have a profound impact in reducing occurrences of blindness and anaemia caused by deficiencies in Vitamin A and iron respectively.
- Scientists have inserted a gene from yeast into the tomato, and the result is a plant whose fruit stays longer on the vine and has an extended shelf life.

### ***Development of Drought resistance varieties***

- Progress has been made in developing cereal varieties that have a greater tolerance for soil alkalinity, free aluminium and iron toxicities.
- These varieties will allow agriculture to succeed in poorer soil areas, thus adding more land to the global production base.
- Research is also in progress to produce crop varieties capable of tolerating reduced water conditions.

## **Veterinary Science**

- Sequencing projects of many farm animals including cows, pigs and sheep are now well under way in the hope that a better understanding of the biology of these organisms will have huge impacts for improving the production and health of livestock and ultimately have benefits for human nutrition.

## **Comparative Studies**

- Analysing and comparing the genetic material of different species is an important method for studying the functions of genes, the mechanisms of inherited diseases and species evolution.
- Bioinformatics tools can be used to make comparisons between the numbers, locations and biochemical functions of genes in different organisms.

**BLAST:** The introduction of BLAST, or The Basic Local Alignment Search Tool, in 1990 made it easier to rapidly scan huge databases for homologies, or sequence similarity, and to statistically evaluate the resulting matches. BLAST works by comparing a user's unknown sequence against the database of all known sequences to determine likely matches. Sequence similarities found by BLAST have been critical in several gene discoveries. Hundreds of major sequencing centers and research institution around the country use this software to transmit a query sequence from their local computer to BLAST server at the NCBI via the Internet. In a matter of seconds the BLAST server compares the user's sequence with up to million known sequences and determines the closest matches. BLAST enables not only locating the orthologous or homologous sequences derived from a common ancestor but also provides a statistical scores (such as E values and similarity scores) to validate the search results. The sequence similarity search tool BLAST comes in different flavors—BLASTn (for DNA sequences), BLASTp (Protein sequences). Similar to BLAST there are also numerous similarity search tools exist such as FASTA, WUBLAST and PSI-BLAST, which basically differ in efficiency of search. Almost all these tools are based on computer technique called Pattern search employed by algorithms like Smith-Waterman (<http://www.med.nyu.edu/rcr/rcr/course/sim-sw.html>) and Needleman & Wunsch (<http://www.gen.tcd.ie/molevol/nwswat.html>) employed in design of various types of BLAST tools. Not all significant homologies are readily and easily detected. Some of the most interesting

are subtle similarities that do not always rise to statistical significance during a standard BLAST search. Therefore, NCBI has extended the statistical methodology used in the original BLAST to address the problem of detecting weak, yet significant, sequence similarities. PSIBLAST, or Position Specific Iterated BLAST, searches sequence databases with a profile constructed using BLAST alignments, from which it then constructs what is called a position specific score matrix. For protein analysis, the new Pattern Hit Initiated BLAST, or PHI-BLAST serves to complement the profile based searching that was previously introduced with PSI-BLAST. PHI-BLAST further incorporates hypotheses as to the biological function of a query sequence and restrict the analysis to a set of protein sequences that are already known to contain a specific pattern or motif.

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*Specialized BLASTs are also available for human, microbial, and other genomes, as well as for vector contamination, immunoglobulins, and tentative human consensus sequences.*

**RPS-BLAST** is a “reverse” version of PSIBLAST, which has been described above. Both RPS-BLAST and PSI-BLAST use similar methods to derive conserved features of a protein family. However, RPS-BLAST compares a query sequence against a database of profiles prepared from ready-made alignments whereas PSI-BLAST builds alignment starting from a single protein sequence. The programs also differ in purpose: RPS-BLAST is used to identify conserved domains in a query sequence, whereas PSI-BLAST is used to identify other members of the protein family to which a query sequence belongs.

**VAST**, or Vector Alignment Search Tool, is a computer algorithm developed at NCBI for use in identifying similar three dimensional protein structures. VAST is capable of detecting structural similarities between proteins stored in MMDB even when no sequence similarity is detected.

**VAST Search** is NCBI’s structure-structure similarity search service that compares threedimensional coordinates of newly determined protein structures to those in the MMDB or PDB databases. VAST Search creates a list of structure neighbors or related structures that a user can then browse interactively. VAST search will retrieve almost all structures with an identical three-dimensional fold although it may occasionally miss a few structures or report chance similarities.

**Bioinformaticians** handle a large amount of data: in TBs if not in gigs thus it becomes important not only to store such massive data but also making sense out of them. In this article, I will talk about what is data mining and how bioinformaticians can benefit from it.

### **What is data mining?**

Data Mining is the process of discovering a new data/pattern/information/understandable models from huge amount of data that already exists. It is sometimes also referred to as "Knowledge Discovery in Databases" (KDD). It has been successfully applied in bioinformatics which is data-rich and requires essential findings such as gene expression, protein modeling, drug discovery and so on. Development of novel data mining methods provides a useful way to understand the rapidly expanding biological data. Now let's discuss basic concepts of data mining and then we will move to its application in bioinformatics. I will also discuss some data mining tools in upcoming articles.

As defined earlier, data mining is a process of automatic generation of information from existing data. The major goals of data mining are "prediction" & "description". The main tasks which can be performed with it are as follows:

§ **Classification:** Classification is the learning of a function that maps / reads (classifies) the input data item into one of several predefined classes (i.e., existing data).

§ **Estimation:** It shows a value for the data input.

§ **Prediction:** Involves both classification and estimation, but the data is classified on the basis of the some future behavior or estimated future value.

§ **Association rules:** It is also known as dependency modeling, where it determines the data associated with each other and what may be the outcomes.

§ **Clustering:** Separating the population into subgroups or clusters.

§ **Description & Visualization:** Representing the data with the help of visualization techniques / tools.

Data learning is composed of two main categories:

Directed (Supervised) learning and Indirected (Unsupervised) learning.

Classification, Estimation and Prediction falls under the category of Supervised learning and the rest three tasks- Association rules, Clustering and Description & Visualization comes under the Unsupervised learning. In the former category, some

*relationships are established among all the variables and the patterns are identified in the later category.*

*Data Mining has been proved to be very effective and useful in bioinformatics, such as, microarray analysis, gene finding, domain identification, protein function prediction, disease identification, drug discovery and so on.*

### **FASTA and BLAST**

- *The number of DNA and protein sequences in public databases is very large.*
- *Searching a database involves aligning the query sequence to each sequence in the database, to find significant local alignment.*
- *BLAST and FASTA are two similarity searching programs that identify homologous DNA sequences and proteins based on the excess sequence similarity.*
- *They provide facilities for comparing DNA and proteins sequences with the existing DNA and protein databases.*
- *They are two major **heuristic algorithms** for performing database searches.*

### ***Working of FASTA and BLAST***

- *FASTA and BLAST are the software tools used in bioinformatics. Both BLAST and FASTA use a heuristic word method for fast pairwise sequence alignment.*
- *It works by finding short stretches of identical or nearly identical letters in two sequences. These short strings of characters are called words.*
- *The basic assumption is that two related sequences must have at least one word in common.*
- *By first identifying word matches, a longer alignment can be obtained by extending similarity regions from the words.*
- *Once regions of high sequence similarity are found, adjacent high-scoring regions can be joined into a full alignment.*

*The main difference between BLAST and FASTA is that BLAST is mostly involved in finding of ungapped, locally optimal sequence alignments whereas FASTA is involved in finding similarities between less similar sequences.*

### ***BLAST (Basic Local Alignment Search Tool)***

- *The BLAST program was developed by Stephen Altschul of NCBI in 1990 and has since become one of the most popular programs for sequence analysis.*
- *BLAST uses heuristics to align a query sequence with all sequences in a database.*
- *The objective is to find high-scoring ungapped segments among related sequences. The existence of such segments above a*

given threshold indicates pairwise similarity beyond random chance, which helps to discriminate related sequences from unrelated sequences in a database.

- *BLAST* is popular as a bioinformatics tool due to its ability to identify regions of local similarity between two sequences quickly. *BLAST* calculates an expectation value, which estimates the number of matches between two sequences. It uses the local alignment of sequences.

## **Variants of BLAST**

- **BLAST-N:** compares nucleotide sequence with nucleotide sequences
- **BLAST-P:** compares protein sequences with protein sequences
- **BLAST-X:** Compares nucleotide sequences against the protein sequences
- **tBLAST-N:** compares the protein sequences against the six frame translations of nucleotide sequences
- **tBLAST-X:** Compares the six frame translations of nucleotide sequence against the six frame translations of protein sequences.

## **FASTA**

- FASTA stands for fast-all" or "FastA".
- It was the first database similarity search tool developed, preceding the development of BLAST.
- FASTA is another sequence alignment tool which is used to search similarities between sequences of DNA and proteins.
- FASTA uses a "hashing" strategy to find matches for a short stretch of identical residues with a length of k. The string of residues is known as ktuples or ktups, which are equivalent to words in BLAST, but are normally shorter than the words.
- Typically, a ktup is composed of two residues for protein sequences and six residues for DNA sequences.
- The query sequence is thus broken down into sequence patterns or words known as k-tuples and the target sequences are searched for these k-tuples in order to find the similarities between the two.
- FASTA is a fine tool for similarity searches.

These methods are not guaranteed to find the optimal alignment or true homologs, but are 50–100 times faster than dynamic programming.

## HIV

HIV or AIDS The human immunodeficiency virus (HIV) is the cause of one of the most destructive human pandemics in recorded history. Since it was first recognized in 1981 it has killed more than 25 million people. Conservative estimates suggest that 33 million people are currently infected: 60% of them live in sub-Saharan Africa. In the UK in 2007 there were 77,400 HIV positive people and the rates of new HIV diagnoses have continued to rise in each of the last 25 years. There is often confusion between the terms AIDS and HIV. Acquired immune deficiency syndrome (AIDS) is a set of symptoms that occur in the final stage of an infection caused by the human immunodeficiency virus (HIV). AIDS occurs when the virus has destroyed the immune system, leaving the patient highly susceptible to other life threatening infections. People who are infected with HIV are referred to as being 'HIV positive', but they do not necessarily have any symptoms of disease. With the advent of new drug regimes it is now hoped that many HIV positive people may never reach the AIDS stage.

### What is HIV?

HIV is an RNA virus known as a retrovirus. The HIV virion has a central core containing two identical RNA genomes and enzymes such as reverse transcriptase, protease and integrase. There is a protein capsid covered by a lipid bilayer envelope which contains glycoprotein spikes. There are two major strains of HIV. HIV-1 causes the majority of the infections worldwide and is more easily transmitted than the other strain HIV-2. HIV-2 is restricted to West Africa, although there are imported cases in the UK.

### Signs and symptoms

The symptoms of HIV vary depending on the stage of infection. Though people living with HIV tend to be most infectious in the first few months after being infected, many are unaware of their status until the later stages. In the first few weeks after initial infection people may experience no symptoms or an influenza-like illness including fever, headache, rash or sore throat.

As the infection progressively weakens the immune system, they can develop other signs and symptoms, such as swollen lymph nodes, weight loss, fever, diarrhoea and cough. Without treatment, they could also develop severe illnesses such as tuberculosis (TB), cryptococcal meningitis, severe bacterial infections, and cancers such as lymphomas and Kaposi's sarcoma.

## **HIV infection and replication**

HIV only infects white blood cells which have a specific receptor protein on their surface. This is called CD4 and is found on lymphocytes called T-helper cells (CD4+ cells) and certain other cells such as dendritic cells and macrophages. The CD4 receptor is normally involved in antigen recognition but HIV 'hijacks' it in order to get into the cell.

- HIV binds to CD4 receptor on cell surface
- The nucleocapsid containing RNA and reverse transcriptase is inserted into the cell
- Complementary single stranded DNA (cDNA) molecules are made using the RNA as a template
- The cDNA hybridises to make double stranded DNA
- The viral DNA integrates into the host genome
- Viral RNA and proteins are synthesised
- New HIV particles are assembled
- HIV leaves the cell by budding (acquiring its envelope in the process)
- This disrupts the cell membrane, leading to lysis and cell death

## **How is HIV transmitted?**

The three main routes for HIV transmission are:

- Contaminated blood (for example between injecting drug users)
- Sex: vaginal, anal (and very rarely, oral)
- From mother to child (either in pregnancy, during birth or via breastmilk)

Worldwide, approximately 60% of new HIV infections are contracted through sex between men and women. The other cases are usually due to:

- Babies who acquire the virus from their mothers (10%)
- Drug users sharing used needles (10%)
- Sex between men (5-10%) In the early stages of the epidemic, some transmission occurred in health care settings, for example via infected blood for transfusion. This is now rare due to better screening and increased awareness.

## **Diagnosis**

HIV can be diagnosed through rapid diagnostic tests that provide same-day results. This greatly facilitates early diagnosis and linkage with treatment and care. People can also use HIV self-tests to test themselves. However, no single test can provide a full HIV diagnosis; confirmatory testing is required, conducted by a qualified and trained health or community worker at a community centre or clinic. HIV infection can be detected with great accuracy using WHO prequalified tests within a nationally approved testing strategy.

Most widely-used HIV diagnostic tests detect antibodies produced by the person as part of their immune response to fight

HIV. In most cases, people develop antibodies to HIV within 28 days of infection. During this time, people experience the so-called "window" period – when HIV antibodies haven't been produced in high enough levels to be detected by standard tests and when they may have had no signs of HIV infection, but also when they may transmit HIV to others. After infection, an individual may transmit HIV transmission to a sexual or drug-sharing partner or for pregnant women to their infant during pregnancy or the breastfeeding period.

Following a positive diagnosis, people should be retested before they are enrolled in treatment and care to rule out any potential testing or reporting error. Notably, once a person diagnosed with HIV and has started treatment they should not be retested.

While testing for adolescents and adults has been made simple and efficient, this is not the case for babies born to HIV-positive mothers. For children less than 18 months of age, serological testing is not sufficient to identify HIV infection – virological testing must be provided as early as birth or at 6 weeks of age). New technologies are now becoming available to perform this test at the point of care and enable same-day results, which will accelerate appropriate linkage with treatment and care.

### **Treating HIV**

There is currently still no cure for HIV infection, or a vaccine to prevent it. Infection does not have to be seen as a death sentence. Doctors now have an arsenal of drugs to control the infection and increase the average life expectancy of HIV positive people. The drug regime that infected people require is called combination therapy and uses three or more anti-retroviral drugs (ARVs). It is also known as HAART (Highly Active Anti-Retroviral Therapy).

There are currently three kinds of HIV drugs available, all of which have a different mode of action:

**Reverse transcriptase inhibitors (RTIs)** block the role of reverse transcriptase in DNA synthesis and prevent the virus replicating. There are several different types sometimes categorised by the common names of 'nukes' and 'non-nukes'.

**Protease inhibitors (PIs)** also prevent viral replication, this time by inhibiting the action of a protease enzyme involved in the production of new viruses.

**Entry inhibitors (EI)** are a relatively new class of drug which prevents HIV from binding to a co-receptor on the host cell. The combination therapy usually involves two 'nukes' plus either a 'non-nuke' or a protease inhibitor.

Other types of drugs (for example antibiotics) are also used to treat the opportunistic infections associated with the Phase Three or Crisis Stage of AIDS. Many patients find it extremely difficult to stick to complex drug regimes but 'treatment adherence' is vitally important to reduce the chances of drug resistance and keep the infection under control

### **Vaccines**

A vaccine would be the best way to prevent HIV infection and halt the pandemic, but this goal has been elusive. There are

many possible types of experimental HIV vaccines, although none have successfully passed a phase three clinical trial.

## **Prevention**

Individuals can reduce the risk of HIV infection by limiting exposure to risk factors. Key approaches for HIV prevention, which are often used in combination, are listed below.

### **Male and female condom use**

Correct and consistent use of male and female condoms during vaginal or anal penetration can protect against the spread of STIs, including HIV. Evidence shows that male latex condoms when used consistently have an 85% or greater protective effect against HIV and other STIs.

### **Testing and counselling for HIV and STIs**

Testing for HIV and other STIs is strongly advised for all people exposed to any of the risk factors. This enables people to learn of their own HIV status and access necessary prevention and treatment services without delay. WHO also recommends offering testing for partners or couples. Additionally, WHO recommends voluntary assisted partner notification approaches, in which people with HIV receive support to inform their partners either on their own, or with the help of health care providers. Programmes that offer support for testing people in social networks can also be an effective and acceptable approach for some populations.

### **Testing and counselling, linkages to tuberculosis (TB) care**

TB is the most common illness among people living with HIV. Fatal if undetected or untreated, TB is the leading cause of death among people with HIV, responsible for nearly 1 in 3 HIV-associated deaths.

Early detection of TB and prompt linkage to TB treatment and ART can prevent these deaths. TB screening should be offered routinely at HIV care services, and routine HIV testing should be offered to all patients with presumptive and diagnosed TB. TB preventive therapy should be offered to all people living with HIV who do not have active TB. Individuals who are diagnosed with HIV and active TB should urgently start effective TB treatment (including for multidrug-resistant TB) and ART.

### **Voluntary medical male circumcision (VMMC)**

Medical male circumcision reduces the risk of heterosexually acquired HIV infection in men by approximately 50% including in 'real world' settings where scale up occurred alongside the increasing coverage of ART with its secondary prevention effect. In 2020, WHO updated the 2007 recommendation for VMMC to continue as an additional prevention intervention among males age 15 years and older. This is a key intervention of a combination prevention strategy in settings with high HIV prevalence, particularly countries in eastern and southern Africa. VMMC also reduces the risk of other sexually transmitted infections. At the end of 2019, 27 million adolescent boys and men in eastern and southern

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Africa had been provided with a package of services. Over 15 million VMMCs were performed between 2016 and 2019. The service package, includes education on safer sex and condom use, offer of HIV testing, management of sexually transmitted infections in including links to treatment as needed, and the surgical procedure. VMMC is regarded as a good point of contact between men and adolescent boys and health services, which they often do not seek out; and other services such as hypertension screening are offered in some settings.

## **Use of ARVs for prevention**

### **Secondary prevention benefits of ART**

Several studies confirmed that if an HIV-positive person is taking ART and is virally suppressed they do not transmit HIV to their uninfected sexual partners WHO recommended that all people living with HIV should be offered ART with the main aim of saving lives and contributing to reducing HIV transmission.

### **Pre-exposure prophylaxis (PrEP) for HIV-negative partner**

Oral PrEP of HIV is the daily use of ARVs by HIV-negative people to block the acquisition of HIV. More than 10 randomized controlled studies have demonstrated the effectiveness of PrEP in reducing HIV transmission among a range of populations, including serodiscordant heterosexual couples (where one partner is infected and the other is not), men who have sex with men, transgender women, high-risk heterosexual couples, and people who inject drugs.

WHO recommends PrEP as a prevention choice for people at substantial risk of HIV infection as part of a combination of prevention approaches. WHO has also expanded these recommendations to HIV-negative women who are pregnant or breastfeeding. For men who have sex with men “event driven” PrEP is also an effective PrEP option. This is taking two pills sex between two and 24 hours in before sex; then, a third pill 24 hours after the first two pills, and a fourth pill 48 hours after the first two pills. This is often known as the 2+1+1. Long acting PrEP products including an injection and a vaginal ring show promise and WHO will continue to review the data on these for future guidance.

### **Post-exposure prophylaxis for HIV (PEP)**

PEP is the use of ARVs within 72 hours of exposure to HIV to prevent infection. PEP includes counselling, first aid care, HIV testing, and administration of a 28-day course of ARV drugs with follow-up care. The WHO recommends PEP use for both occupational and non-occupational exposures, and for adults and children.

### **Harm reduction for people who inject and use drugs**

People who inject drugs can take precautions against becoming infected with HIV by using sterile injecting equipment (including needles and syringes) for each injection, and not sharing drug-using equipment and drug solutions. Treatment of drug dependence, in particular, opioid substitution therapy for people dependent on opioids, also helps to reduce the risk of HIV transmission and supports adherence to HIV treatment. A comprehensive package of HIV prevention and treatment interventions for people who inject drugs includes:

- needle and syringe programmes;
- opioid substitution therapy for people dependent on opioids, and other evidence-based drug dependence treatment;
- HIV testing and counselling;
- HIV treatment and care;
- risk-reduction information and education, and provision of naloxone to prevent opioid overdose;
- access to condoms; and
- management of STIs, TB and viral hepatitis.

### **Elimination of mother-to-child transmission of HIV**

The transmission of HIV from an HIV-positive mother to her child during pregnancy, labour, delivery or breastfeeding is called vertical or mother-to-child transmission (MTCT). In the absence of any interventions during these stages, rates of HIV transmission from mother-to-child can be between 15% and 45%. The risk of MTCT can almost be eliminated if both the mother and her baby are provided with ARV drugs as early as possible in pregnancy and during the period of breastfeeding.

WHO recommends lifelong ART for all people living with HIV, regardless of their CD4 count and the clinical stage of disease; this includes pregnant and breastfeeding women. In 2019, 85% of the estimated 1.3 million pregnant women living with HIV globally received ARV drugs to prevent transmission to their children. A growing number of countries and territories are achieving very low rates of MTCT, with some formally validated for elimination of MTCT of HIV as a public health problem (Anguilla, Antigua and Barbuda, Armenia, Belarus, Bermuda, Cayman Islands, Cuba, Malaysia, Maldives, Montserrat, Saint Kitts and Nevis, and Thailand). Several countries with a high burden of HIV infection are also progressing along the path to elimination.

### **DIABETES MELLITUS**

#### **What is Diabetes?**

With diabetes, your body either doesn't make enough insulin or can't use it as well as it should. Diabetes is a chronic (long-lasting) health condition that affects

how your body turns food into energy. Most of the food you eat is broken down into sugar (also called glucose) and released into your bloodstream. When your blood sugar goes up, it signals your pancreas to release insulin. Insulin acts like a key to let the blood sugar into your body's cells for use as energy.

If you have diabetes, your body either doesn't make enough insulin or can't use the insulin it makes as well as it should. When there isn't enough insulin or cells stop responding to insulin, too much blood sugar stays in your bloodstream.

Over time, that can cause serious health problems, such as heart, and kidney disease.

About 422 million people worldwide have diabetes, the majority living in low-and middle-income countries, and 1.6 million deaths are directly attributed to diabetes each year. Both the number of cases and the prevalence of diabetes have been steadily increasing over the past few decades.

There isn't a cure yet for diabetes, but losing weight, eating healthy food, and being active can really help. Taking medicine as needed and keeping health care appointments can also reduce the impact of diabetes on your life.

## **Types of Diabetes**

There are three main types of diabetes: type 1, 2, and Gestational diabetes (diabetes while pregnant).

### **Type 1 Diabetes**

Type 1 diabetes is thought to be caused by an autoimmune reaction (the body attacks itself by mistake) that stops your body from making insulin. Approximately 5-10% of the people who have diabetes have type 1. Symptoms of type 1 diabetes often develop quickly. It's usually diagnosed in children, teens, and young adults. If you have type 1 diabetes, you'll need to take insulin every day to survive. Currently, no one knows how to prevent type 1 diabetes.

#### ***What Causes Type 1 Diabetes?***

Type 1 diabetes is thought to be caused by an autoimmune reaction (the body attacks itself by mistake) that destroys the cells in the pancreas that make insulin, called beta cells. This process can go on for months or years before any symptoms appear.

Some people have certain genes (traits passed on from parent to child) that make them more likely to develop type 1 diabetes, though many won't go on to have type 1 diabetes even if they have the genes. Being exposed to a trigger in the environment, such as a virus, is also thought to play a part in developing type 1 diabetes. Diet and lifestyle habits don't cause type 1 diabetes.

#### ***Symptoms and Risk Factors***

It can take months or years for enough beta cells to be destroyed before symptoms of type 1 diabetes are noticed. Type 1 diabetes symptoms can develop in just a few weeks or months. Once symptoms appear, they can be severe.

Some type 1 diabetes symptoms are similar to symptoms of other health conditions. Don't guess—if you think you could have type 1 diabetes, see your doctor right away to get your blood sugar tested. Untreated diabetes can lead to very serious—even fatal—health problems.

Risk factors for type 1 diabetes are not as clear as for prediabetes and type 2 diabetes, though family history is known to play a part.

## ***Testing for Type 1 Diabetes***

A simple blood test will let you know if you have diabetes. If you've gotten your blood sugar tested at a health fair or pharmacy, follow up at a clinic or doctor's office to make sure the results are accurate.

If your doctor thinks you have type 1 diabetes, your blood may also be tested for autoantibodies (substances that indicate your body is attacking itself) that are often present with type 1 diabetes but not with type 2. You may have your urine tested for ketones (produced when your body burns fat for energy), which also indicate type 1 diabetes instead of type 2.

## ***Managing Diabetes***

Unlike many health conditions, diabetes is managed mostly by you, with support from your health care team (including your primary care doctor, foot doctor, dentist, eye doctor, registered dietitian nutritionist, diabetes educator, and pharmacist), family, teachers, and other important people in your life. Managing diabetes can be challenging, but everything you do to improve your health is worth it!

If you have type 1 diabetes, you'll need to take insulin shots (or wear an insulin pump) every day to manage your blood sugar levels and get the energy your body needs. Insulin can't be taken as a pill because the acid in your stomach would destroy it before it could get into your bloodstream. Your doctor will work with you to figure out the most effective type and dosage of insulin for you.

You'll also need to check your blood sugar regularly. Ask your doctor how often you should check it and what your target blood sugar levels should be. Keeping your blood sugar levels as close to target as possible will help you prevent or delay diabetes-related complications.

Stress is a part of life, but it can make managing diabetes harder, including managing your blood sugar levels and dealing with daily diabetes care. Regular physical activity, getting enough sleep, and relaxation exercises can help. Talk to your doctor and diabetes educator about these and other ways you can manage stress.

Healthy lifestyle habits are really important, too:

- Making [healthy food choices](#)
- Being [physically active](#)
- Controlling your [blood pressure](#)
- Controlling your [cholesterol](#)

Make regular appointments with your health care team to be sure you're on track with your treatment plan and to get help with new ideas and strategies if needed.

Whether you just got diagnosed with type 1 diabetes or have had it for some time, meeting with a diabetes educator is a great way to get support and guidance, including how to:

- Develop and stick to a healthy eating and activity plan

- Test your blood sugar and keep a record of the results
- Recognize the signs of high or low blood sugar and what to do about it
- Give yourself insulin by syringe, pen, or pump
- Monitor your feet, skin, and eyes to catch problems early
- Buy diabetes supplies and store them properly
- Manage stress and deal with daily diabetes care

## ***Hypoglycemia***

[Hypoglycemia](#)

[external icon](#)

(low blood sugar) can happen quickly and needs to be treated immediately. It's most often caused by too much insulin, waiting too long for a meal or snack, not eating enough, or getting extra physical activity. Hypoglycemia symptoms are different from person to person; make sure you know your specific symptoms, which could include:

- Shakiness
- Nervousness or anxiety
- Sweating, chills, or clamminess
- Irritability or impatience
- Dizziness and difficulty concentrating
- Hunger or nausea
- Blurred vision
- Weakness or fatigue
- Anger, stubbornness, or sadness

If you have hypoglycemia several times a week, talk to your doctor to see if your treatment needs to be changed.

## **Type 2 Diabetes**

With type 2 diabetes, your body doesn't use insulin well and can't keep blood sugar at normal levels. About 90-95% of people with diabetes have type 2. It develops over many years and is usually diagnosed in adults (but more and more in children, teens, and young adults). You may not notice any symptoms, so it's important to get your blood sugar tested if you're at risk. Type 2 diabetes can be prevented or delayed with healthy lifestyle changes, such as losing weight, eating healthy food, and being active.

## ***What Causes Type 2 Diabetes?***

Insulin is a hormone made by your pancreas that acts like a key to let blood sugar into the cells in your body for use as energy. If you have type 2 diabetes, cells don't respond normally to insulin; this is called insulin resistance. Your pancreas makes more insulin to try to get cells to respond. Eventually your pancreas can't keep up, and your blood sugar rises, setting the stage for prediabetes and type 2 diabetes. High blood sugar is damaging to the body and can cause other serious health problems.

## ***Symptoms and Risk Factors***

Type 2 diabetes symptoms often develop over several years and can go on for a long time without being noticed (sometimes there aren't any noticeable symptoms at all). Because symptoms can be hard to spot, it's important to know the risk factors and to see your doctor to get your blood sugar tested if you have any of them.

## ***Testing for Type 2 Diabetes***

A simple blood test will let you know if you have diabetes. If you've gotten your blood sugar tested at a health fair or pharmacy, follow up at a clinic or doctor's office to make sure the results are accurate.

## ***Managing Diabetes***

Unlike many health conditions, diabetes is managed mostly by you, with support from your health care team (including your primary care doctor, foot doctor, dentist, eye doctor, registered dietitian nutritionist, diabetes educator, and pharmacist), family, and other important people in your life. Managing diabetes can be challenging, but everything you do to improve your health is worth it!

Stress is a part of life, but it can make managing diabetes harder, including managing your blood sugar levels and dealing with daily diabetes care. Regular physical activity, getting enough sleep, and relaxation exercises can help. Talk to your doctor and diabetes educator about these and other ways you can manage stress.

Make regular appointments with your health care team to be sure you're on track with your treatment plan and to get help with new ideas and strategies if needed.

Whether you were just diagnosed with diabetes or have had it for some time, meeting with a diabetes educator is a great way to get support and guidance, including how to:

- Develop a healthy eating and activity plan
- Test your blood sugar and keep a record of the results
- Recognize the signs of high or low blood sugar and what to do about it
- If needed, give yourself insulin by syringe, pen, or pump
- Monitor your feet, skin, and eyes to catch problems early

- 
- Buy diabetes supplies and store them properly
  - Manage stress and deal with daily diabetes care

## **Type 2 Diabetes in Children and Teens**

Childhood obesity rates are rising, and so are the rates of type 2 diabetes in youth. More than 75% of children with type 2 diabetes have a close relative who has it, too. But it's not always because family members are related; it can also be because they share certain habits that can increase their risk. Parents can help prevent or delay type 2 diabetes by developing a plan for the whole family:

- Drinking more water and fewer sugary drinks
- Eating more fruits and vegetables
- Making favorite foods healthier
- Making physical activity more fun

Healthy changes become habits more easily when everyone makes them together. Find out how to take charge family style with these healthy tips

## **Gestational Diabetes**

Gestational diabetes develops in pregnant women who have never had diabetes. If you have gestational diabetes, your baby could be at higher risk for health problems. Gestational diabetes usually goes away after your baby is born but increases your risk for type 2 diabetes later in life. Your baby is more likely to have obesity as a child or teen, and more likely to develop type 2 diabetes later in life too.

## **Prediabetes**

In the United States, 88 million adults—more than 1 in 3—have prediabetes. What's more, more than 84% of them don't know they have it. With prediabetes, blood sugar levels are higher than normal, but not high enough yet to be diagnosed as type 2 diabetes. Prediabetes raises your risk for type 2 diabetes, heart disease, and stroke. The good news is if you have prediabetes, a CDC-recognized life style changing program can help you take healthy steps to reverse it.

## **Structure of Coronavirus**

- Coronaviruses fall in the virus family *Coronaviridae*, order *Nidovirales*.
- Coronaviruses are enveloped, 120 to 160 nm particles that contain an unsegmented genome of single-stranded positive-sense RNA (27–32 kb).
- The large, plus-stranded [RNA](#) genome associates with the N protein to form a helical nucleocapsid.
- The helical nucleocapsid is 9–11 nm in diameter.
- There are 20 nm long club or petal-shaped projections that are widely spaced on the outer surface of the envelope, suggestive of a solar corona.
- The viral structural proteins include a 50–60 kDa phosphorylated nucleocapsid (N) protein, a 20–35 kDa membrane (M) glycoprotein that serves as a matrix protein embedded in the envelope lipid bilayer and interacting with the nucleocapsid, and the spike (S) a 180–220 kDa glycoprotein that makes up the petal-shaped peplomers.
- Some viruses, including human coronavirus OC43 (HCoV-OC43), contain a third glycoprotein (HE; 65 kDa) that causes hemagglutination and has acetyl esterase activity.

## **Genome of Coronavirus**

- Coronavirus genomes are monopartite, single-stranded, positive-sense, polyadenylated, and capped RNAs ranging from 27 to 32 kb in length.
- The 5' approximately 20 to 22 kb carries the replicase gene, which encodes multiple enzymatic activities.
- The replicase gene products are encoded within two very large open reading frames, ORFs 1a and 1b.
- The order of the genes encoding the viral RNA-dependent RNA polymerase and the four common structural proteins, the spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins are indicated as Pol-S-E-M-N.
- Coronavirus genomes also include a variety of additional open reading frames (ORFs) that encode two to four nonstructural proteins of unknown functions.
- In the genome, a common intergenic sequence (IS) of about 7 bases is found at the 5' end of each gene.

- This IS sequence is essential for the formation of subgenomic RNAs.
- Coronavirus-infected cells contain multiple overlapping subgenomic, capped, and polyadenylated mRNAs with a common 3' end.
- Each subgenomic mRNA and the viral genomic RNA, which also serves as an mRNA, is translated to yield only the protein encoded by the 5' gene on the mRNA.

## **Epidemiology of Coronavirus**

- Natural outbreaks of colds caused by coronaviruses occur predominantly during the winter months, although in children, two peaks in late autumn to early winter and early summer were detected.
- It is estimated that coronaviruses cause 15–30% of all colds.
- Studies using virus detection or serology have shown that HCoV 229E, OC43, and NL63 occur worldwide.
- The contribution of each HCoV may vary widely from year to year, for example, 229E contributing as little as 1% to acute respiratory infections in the community in one year and up to 35% in the next.
- The incidence of coronavirus infections varies markedly from year to year, ranging in one 3-year study from 1% to 35%.

## **Novel coronavirus 2019 (SARS-CoV-2)**

- A novel coronavirus known as SARS-CoV-2 was identified in Wuhan, China when people developed pneumonia-like symptoms.
- SARS-CoV-2 could transmit from one human to another human.

## **Replication of Coronavirus**

- Natural infection of humans with human respiratory coronaviruses occurs through exposure to respiratory secretions.
- Coronaviruses attach to their glycoprotein receptors on host cells via their S proteins.
- Viral entry is mediated by fusion of the viral envelope with the host cell membrane or by receptor-mediated endocytosis.
- Group 1 coronaviruses 229E and NL63 bind to the metalloproteases, human aminopeptidase N and angiotensin-converting enzyme 2 (ACE-2) respectively.
- The receptors for OC43 and HKU-1 have not been yet identified.
- The fusion of the viral and cell membranes (either at the cell surface or within the endocytic vesicle) is mediated by the S2

*portion of the virus spike protein which functions as a class 1 fusion protein.*

- *Once the viral RNA is released into the cytoplasm, translation of the positive-strand genomic RNA gives rise to a large polyprotein that undergoes proteolytic processing to generate an RNA-dependent RNA polymerase.*
- *An RNA-dependent RNA polymerase translated from the plus-stranded viral genomic RNA makes a negative-strand that serves as the template for a nested set of five to seven subgenomic mRNAs.*
- *Translation of subgenomic mRNAs gives rise to structural viral proteins.*
- *The N protein and newly synthesized genomic RNA assemble to form helical nucleocapsids.*
- *Membrane glycoprotein M is inserted in the endoplasmic reticulum (ER) and anchored in the Golgi apparatus.*
- *The nucleocapsid (N plus genomic RNA) binds to M protein at the budding compartment (ERGIC).*
- *E and M proteins interact to trigger the budding of virions, enclosing the nucleocapsid.*
- *These newly formed virions are transported via the Golgi apparatus to the plasma membrane where they are released by exocytosis.*

### ***Pathogenesis of Coronavirus***

- *The primary route of transmission of human coronaviruses is via the respiratory tract, most likely spread by aerosols and in large droplets (e.g., sneezes).*
- *Infection with the common-cold coronaviruses leads to loss of ciliary action (ciliostasis) and degenerative changes affecting the cilia of epithelial cells of the respiratory tract.*
- *Infection remains localized to the upper respiratory tract because the optimum temperature for viral growth is 33° C to 35° C and may lead to the lower respiratory tract.*
- *HCoV-OC43 is generally associated with mild upper respiratory tract infections, although it has been shown to have neuroinvasive properties.*

### ***Clinical manifestations of Coronavirus***

- *HCoVs in both the 229E- and OC43-related serogroups cause upper respiratory signs and symptoms in adults and children that vary in frequency and severity.*
- *HCoVs cause respiratory infections(bronchiolitis and pneumonia), but gastroenteritis and neurological disorders can also occur.*
- *The human coronaviruses produce “common colds,” usually afebrile, in adults.*
- *The symptoms include nasal discharge and malaise.*

- Other symptoms include rhinorrhea, headache, malaise, chills, sore throat, and cough.
- The incubation period is from 2 to 5 days.
- Symptoms last for a mean of 7 days, with a range of 3 to 18 days.
- Patients with symptomatic coronavirus infection show a rise in neutralizing and complement fixation antibody titers in the serum after inoculation that waned after months.
- The lower respiratory tract is seldom involved, although pneumonia may occur.
- Asthmatic children may suffer wheezing attacks, and respiratory symptoms may be exacerbated in adults with chronic pulmonary disease.
- HCoV-OC43 can infect neurons and cause encephalitis.

### ***Lab Diagnosis of Coronavirus***

**Specimen:** respiratory secretions, stool (HKU1)

- Virus isolation- The human hepatoma cell-line HUH7 has been recently used for primary isolation of OC43, 229E and HKU-1 viruses from clinical specimens and NL63 has been isolated in LLC-MK2 and Vero B4 cells.
- Detection of viral RNA by RT-PCR.
- Electron microscopy of negatively stained stool specimens is useful for the detection of enteric coronaviruses.
- Complement fixation, ELISA assays, immunofluorescence or virus neutralization tests have been used for serological diagnosis.
- The serologic diagnosis of infections with strain 229E is possible using a passive hemagglutination test in which red cells coated with coronavirus antigen are agglutinated by antibody-containing sera.
- HCoV-OC43-related virions that express a HE glycoprotein on the viral envelope can also be detected by hemagglutination and acetyl esterase assays.

### ***Treatment of Coronavirus***

- There is no proven treatment for human coronavirus infections and no vaccine as of 1<sup>st</sup> Oct. 2020.

### ***Prevention and control of Coronavirus***

- Washing hands often with soap and water.
- Avoid touching eyes, nose, or mouth with unwashed hands.
- Avoiding close contact with people who are sick.
- Covering mouth and nose with a tissue while coughing or sneezing, then throw the tissue in the trash and washing hands.

## **What Is Cancer?**

Cancer is the name given to a collection of related diseases. In all types of cancer, some of the body's cells begin to divide without stopping and spread into surrounding tissues. Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Normally, human cells grow and divide to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place.

When cancer develops, however, this orderly process breaks down. As cells become more and more abnormal, old or damaged cells survive when they should die, and new cells form when they are not needed. These extra cells can divide without stopping and may form growths called tumors.

Many cancers form solid tumors, which are masses of tissue. Cancers of the blood, such as leukemias, generally do not form solid tumors.

Cancerous tumors are malignant, which means they can spread into, or invade, nearby tissues. In addition, as these tumors grow, some cancer cells can break off and travel to distant places in the body through the blood or the lymph system and form new tumors far from the original tumor.

Unlike malignant tumors, benign tumors do not spread into, or invade, nearby tissues. Benign tumors can sometimes be quite large, however. When removed, they usually don't grow back, whereas malignant tumors sometimes do. Unlike most benign tumors elsewhere in the body, benign brain tumors can be life threatening.

## **Differences between Cancer Cells and Normal Cells**

Cancer cells differ from normal cells in many ways that allow them to grow out of control and become invasive. One important difference is that cancer cells are less specialized than normal cells. That is, whereas normal cells mature into very distinct cell types with specific functions, cancer cells do not. This is one reason that, unlike normal cells, cancer cells continue to divide without stopping.

In addition, cancer cells are able to ignore signals that normally tell cells to stop dividing or that begin a process known as programmed cell death, or apoptosis, which the body uses to get rid of unneeded cells.

Cancer cells may be able to influence the normal cells, molecules, and blood vessels that surround and feed a tumor—an area known as the microenvironment. For instance, cancer cells can induce nearby normal cells to form blood vessels that supply tumors with oxygen and nutrients, which they need to grow. These blood vessels also remove waste products from tumors.

Cancer cells are also often able to evade the immune system, a network of organs, tissues, and specialized cells that protects the body from infections and other conditions. Although the immune system normally removes damaged or abnormal cells from the body, some cancer cells are able to “hide” from the immune system.

Tumors can also use the immune system to stay alive and grow. For example, with the help of certain immune system cells that normally prevent a runaway immune response, cancer cells can actually keep the immune system from killing cancer cells.

### **How Cancer Arises?**

Cancer is caused by certain changes to genes, the basic physical units of inheritance. Genes are arranged in long strands of tightly packed DNA called chromosomes.

Cancer is a genetic disease—that is, it is caused by changes to genes that control the way our cells function, especially how they grow and divide.

Genetic changes that cause cancer can be inherited from our parents. They can also arise during a person’s lifetime as a result of errors that occur as cells divide or because of damage to DNA caused by certain environmental exposures.

Cancer-causing environmental exposures include substances, such as the chemicals in tobacco smoke, and radiation, such as ultraviolet rays from the sun.

Each person’s cancer has a unique combination of genetic changes. As the cancer continues to grow, additional changes will occur. Even within the same tumor, different cells may have different genetic changes.

In general, cancer cells have more genetic changes, such as mutations in DNA, than normal cells. Some of these changes may have nothing to do with the cancer; they may be the result of the cancer, rather than its cause.

### **"Drivers" of Cancer**

The genetic changes that contribute to cancer tend to affect three main types of genes—proto oncogenes, and DNA repair genes. These changes are sometimes called “drivers” of cancer.

Proto-oncogenes are involved in normal cell growth and division. However, when these genes are altered in certain ways or are more active than normal, they may become cancer-causing genes (or oncogenes), allowing cells to grow and survive when they should not.

Tumor suppressor genes are also involved in controlling cell growth and division. Cells with certain alterations in tumor

suppressor genes may divide in an uncontrolled manner.

DNA repair genes are involved in fixing damaged DNA. Cells with mutations in these genes tend to develop additional mutations in other genes. Together, these mutations may cause the cells to become cancerous.

As scientists have learned more about the molecular changes that lead to cancer, they have found that certain mutations commonly occur in many types of cancer. Because of this, cancers are sometimes characterized by the types of genetic alterations that are believed to be driving them, not just by where they develop in the body and how the cancer cells look under the microscope.

## **When Cancer Spreads**

In metastasis, cancer cells break away from where they first formed (primary cancer), travel through the blood or lymph system, and form new tumors (metastatic tumors) in other parts of the body. The metastatic tumor is the same type of cancer as the primary tumor.

A cancer that has spread from the place where it first started to another place in the body is called metastatic cancer. The process by which cancer cells spread to other parts of the body is called metastasis.

Metastatic cancer has the same name and the same type of cancer cells as the original, or primary, cancer. For example, breast cancer that spreads to and forms a metastatic tumor in the lung is metastatic breast cancer, not lung cancer.

Under a microscope, metastatic cancer cells generally look the same as cells of the original cancer. Moreover, metastatic cancer cells and cells of the original cancer usually have some molecular features in common, such as the presence of specific chromosome changes.

Treatment may help prolong the lives of some people with metastatic cancer. In general, though, the primary goal of treatments for metastatic cancer is to control the growth of the cancer or to relieve symptoms caused by it. Metastatic tumors can cause severe damage to how the body functions, and most people who die of cancer die of metastatic disease.

## **Tissue Changes that Are Not Cancer**

Not every change in the body's tissues is cancer. Some tissue changes may develop into cancer if they are not treated, however. Here are some examples of tissue changes that are not cancer but, in some cases, are monitored:

Hyperplasia occurs when cells within a tissue divide faster than normal and extra cells build up, or proliferate. However, the cells and the way the tissue is organized look normal under a microscope. Hyperplasia can be caused by several factors or conditions, including chronic irritation.

Dysplasia is a more serious condition than hyperplasia. In dysplasia, there is also a buildup of extra cells. But the cells look

abnormal and there are changes in how the tissue is organized. In general, the more abnormal the cells and tissue look, the greater the chance that cancer will form.

Some types of dysplasia may need to be monitored or treated. An example of dysplasia is an abnormal mole (called a dysplastic nevus) that forms on the skin. A dysplastic nevus can turn into melanoma, although most do not.

An even more serious condition is carcinoma in situ. Although it is sometimes called cancer, carcinoma in situ is not cancer because the abnormal cells do not spread beyond the original tissue. That is, they do not invade nearby tissue the way that cancer cells do. But, because some carcinomas in situ may become cancer, they are usually treated.

## **Types of Cancer**

There are more than 100 types of cancer. Types of cancer are usually named for the organs or tissues where the cancers form. For example, lung cancer starts in cells of the lung, and brain cancer starts in cells of the brain. Cancers also may be described by the type of cell that formed them, such as an epithelial cell or a squamous cell.

Here are some categories of cancers that begin in specific types of cells:

### ***Carcinoma***

Carcinomas are the most common type of cancer. They are formed by epithelial cells, which are the cells that cover the inside and outside surfaces of the body. There are many types of epithelial cells, which often have a column-like shape when viewed under a microscope.

Carcinomas that begin in different epithelial cell types have specific names:

Adenocarcinoma is a cancer that forms in epithelial cells that produce fluids or mucus. Tissues with this type of epithelial cell are sometimes called glandular tissues. Most cancers of the breast, colon, and prostate are adenocarcinomas.

Basal cell carcinoma is a cancer that begins in the lower or basal (base) layer of the epidermis, which is a person's outer layer of skin.

Squamous cell carcinoma is a cancer that forms in squamous cells, which are epithelial cells that lie just beneath the outer surface of the skin. Squamous cells also line many other organs, including the stomach, intestines, lungs, bladder, and kidneys. Squamous cells look flat, like fish scales, when viewed under a microscope. Squamous cell carcinomas are sometimes called epidermoid carcinomas.

Transitional cell carcinoma is a cancer that forms in a type of epithelial tissue called transitional epithelium, or urothelium. This tissue, which is made up of many layers of epithelial cells that can get bigger and smaller, is found in the linings of the bladder, ureters, and part of the kidneys (renal pelvis), and a few other organs. Some cancers of the bladder, ureters, and kidneys are transitional cell carcinomas.

## **Sarcoma**

Sarcomas are cancers that form in bone and soft tissues, including muscle, fat, blood vessels, lymph vessels, and fibrous tissue (such as tendons and ligaments).

## **Leukemia**

Cancers that begin in the blood-forming tissue of the bone marrow are called leukemias. These cancers do not form solid tumors. Instead, large numbers of abnormal white blood cells (leukemia cells and leukemic blast cells) build up in the blood and bone marrow, crowding out normal blood cells. The low level of normal blood cells can make it harder for the body to get oxygen to its tissues, control bleeding, or fight infections.

There are four common types of leukemia, which are grouped based on how quickly the disease gets worse (acute or chronic) and on the type of blood cell the cancer starts in (lymphoblastic or myeloid).

## **Lymphoma**

Lymphoma is cancer that begins in lymphocytes (T cells or B cells). These are disease-fighting white blood cells that are part of the immune system. In lymphoma, abnormal lymphocytes build up in lymph nodes and lymph vessels, as well as in other organs of the body.

There are two main types of lymphoma:

Hodgkin lymphoma – People with this disease have abnormal lymphocytes that are called Reed-Sternberg cells. These cells usually form from B cells.

Non-Hodgkin lymphoma – This is a large group of cancers that start in lymphocytes. The cancers can grow quickly or slowly and can form from B cells or T cells.

## **Multiple Myeloma**

Multiple myeloma is cancer that begins in plasma cells, another type of immune cell. The abnormal plasma cells, called myeloma cells, build up in the bone marrow and form tumors in bones all through the body. Multiple myeloma is also called plasma cell myeloma and Kahler disease.

## **Melanoma**

Melanoma is cancer that begins in cells that become melanocytes, which are specialized cells that make melanin (the pigment that gives skin its color). Most melanomas form on the skin, but melanomas can also form in other pigmented tissues, such as the eye.

## ***Brain and Spinal Cord Tumors***

There are different types of brain and spinal cord tumors. These tumors are named based on the type of cell in which they formed and where the tumor first formed in the central nervous system. For example, Brain tumors can be benign (not cancer) or malignant (cancer).

## **Other Types of Tumors**

### **Germ Cell Tumors**

Germ cell tumors are a type of tumor that begins in the cells that give rise to sperm or eggs. These tumors can occur almost anywhere in the body and can be either benign or malignant.

### **Neuroendocrine Tumors**

Neuroendocrine tumors form from cells that release hormones into the blood in response to a signal from the nervous system. These tumors, which may make higher-than-normal amounts of hormones, can cause many different symptoms. Neuroendocrine tumors may be benign or malignant.

### **Carcinoid Tumors**

Carcinoid tumors are a type of neuroendocrine tumor. They are slow-growing tumors that are usually found in the gastrointestinal system (most often in the rectum and small intestine). Carcinoid tumors may spread to the liver or other sites in the body, and they may secrete substances such as serotonin or prostaglandins, causing carcinoid syndrome.