Science Fair
2023-2024
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FJHS
Precision Medicine

Dec. 27, 2023

What is Precision Medicine - Abstract

- Precision Medicine (PM) is also known as personalized medicine.
- PM is a revolutionary approach that aims to provideca targeted treatments.
- Tailoring treatments to a subpopulation who have a common sensitivity or issue to a particular disease
  - ↳ Can also be for similar responses to particular drugs.
- In PM, you are not actually making completely new drugs or medical devices for a patient
  - ↳ PM is about classifying patients into smaller catagories.
- We divide them in ways that:
  - That they differ in their case to a particular disease
  - The biology/prognosis of those diseases that they may develope
  - Or their response to a specific treatment
- In PM, Diagnostic testing is often used.
  - ↳ It tells us the most appropriate therapies for patients based on the context of their genetic content, other molecular or cellular analysis.

Effect:

- It has the opportinity to change healthcare
- Bring in more effective medical intervention.

CONT'D

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Goal of Precision Medicine

- Its main aim is to give each individual / group their own customized healthcare plan.
- Also aims to shift from the one-size fits all aproach
  - PM wants to take into account each individuals genetic makeup, environment, and lifestyle
    - ↳ All of this = more personalized treatments

↓

leads to better health outcomes and cost savings in the long run.

"The right therapy, to the right patient, at the right time."
* PM's motto ↑

How is it different from traditional medicine ?

- Main difference is the PM is made for your body's needs.

Traditional Med:

- Widely used among people of all ages & individuals.
- Use its broad therapies & diagnostic tools to treat common problems patients face.
- Doesn't recognice patients genetic profile which influences overall health & wellness

Precision Med:

- More precise way of treating / diagnosing problems within your body.
- NOT generalized
  - ↳ Accounts your symptoms and genetics
  - ↳ leads for the most optimal outcomes.

Geonomics

Dec. 28, 2023

Geonomics:

- Genes are stretches of DNA that serve as like an instruction manual for your body.
  - ↳ tells it how to make proteins and preform tasks that your body needs.
- The same genes offer differ slightly between people
  - ↳ Bases may be switched, missing, or added here and there.
- Most of these changes have no effect but some may create unusual proteins that increase your risk for certain diseases.
- Some variants can affect how well a med. works on you.
  - May also cause you to have different side effects than someone else.

DNA:

- Stands for Deoxyribonucleic acid
- has a major role in PM
  - Allows a personalized approach to healthcare by providing knowledge on a patients genetic makeup and its influence on disease risk, treatment response, & overall health.

- DNA testing & analysis are crucial
  - ↳ allow for the identification of genetic variants associated with different conditions.
    - ↳ This guides tailored treatment decisions.

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NGS:

- Next-generation sequencing is a tech used for DNA & RNA sequencing & variant/mutation detection
- Can sequence hundreds and thousands of genes or a whole genome in a short time.

- Plays a vital role in PM (especially in Precision oncology).
  ↳ great role in cancer treatment & understanding

- PM uses genomic data to provide the right treatment to the right patient at the right time.
  - NGS enables identifying clinically actionable mutations, guiding the treatment plan based on a persons disease-driving molecular alterations.

This helps match patients to therapies and/or asses disease risk.
  ↳ This aids in patient stratification

RNA seq:

- Uses NGS to provide a shot of the transciptome, which is the complete set of RNA transcripts in a cell.
- Allows the identification & quantification of RNA molecules present in a biological sample, allowing researchers to study:
  - gene expressions, alternative splicing, post-transcriptional modifications, gene fusions, mutations, & changes in gene expression overtime or in diff. experimental conditions.

- RNAseq data can be mixed with other omnics data, such as genomics & proteomics to create a more complete picture of an individuals molecular profile.

CONT'D

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- The high resolution data from RNAseq is crucial for understanding the molecular basis of diseases, identifying potential therapeutic targets, & personalizing treatment stratigies.
  - By analyzing this RNA profiles of the patients we can gain deeper understanding of disease mechanisms; predict patient responses to specific treatments, and develope more effective interventions.

- With all this data on our patients; in the future we may be able to scan specific genes/mutations with other individuals and predict possible health issue that may occur/present later on.

Nibroy

Jan. 6, 2024

Biomarkers

What are they & how do they work:

- Distinct biological indications (cellular, biochemical, or molecular) of a process, event, or condition.
  - It can be measured reliably in tissues, cells or fluids, and can be used to detect early changes in a patients health.

(other words: an objective measure that captures what is happening in an organism at a given moment)

- Many biomarkers come from simple measurments made during a docters visit.
  - ↳ ex. blood pressure or body weight
- Others come from lab tests of blood, urine, or tissues.

** Changes captured at the molecular or cellular level are often done by looking at genes/proteins.

Main biomarkers in PM:

1. Genetic Biomarkers: Biomarkers in genomics involve the study of an individual's genes & their interactions with each other & the environment.
   - Single Nucleotide Polymorphisms (SNPs): Variations in a single nucleotide base in the DNA sequence, which can impact traits & disease susceptibility / disease risks & drug response
   - Copy Number Variations (CNVs): Changes in the number of copies of a particular gene, associated with diseases & drug responses.
   - Gene mutations: Specific alterations in the DNA sequence of a gene that may be linked to diseases or drug responses.

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2. Protein Biomarkers: Biomarkers in proteomics focus on the study of proteins & their functions.
   - Protein Expression levels: Measurement of the quantity of specific proteins, which can indicate disease presence or progression.
   - Enzyme Activity: Assessment of the activity levels of enzymes which can be indicative of certain diseases or drug metabolism
   - Phosphorylation Patterns: Associated with disease states or drug response.
3. RNA Biomarkers: Provide dynamic insights into cellular states and regulatory processes
   - mRNA Expression: Analysis of messenger RNA levels to understand gene expression patterns & identify disease-related changes.
   - MicroRNA: Small RNA molecules that regulate gene expression & serve as biomarkers for diseases.
4. Epigenetic Biomarkers: Measure disease-associated & drug-associated epigenetic alterations.
   ↳ This provides decision support for routine clinical treatment & drug discovery.
   - DNA Methylation: changes in the methylation patterns of DNA, influencing gene expression & maybe serving as markers for disease risk or progression.
   - Histone Modifications: Alterations in the structure of histone proteins, affecting gene regulation.
5. Metabolomic Biomarkers: Study of small molecules & metabolites in biological systems.
   - Metabolite Profiles: Analysis of small molecules involved in cellular processes, giving insight into metabolic pathways & disease states.
   - Drug Metabolites: Indicate drug response or toxicity.

6. ctDNA:
Liquid biopsies: Detection & analysis of tumor-derived genetic material circulating in the bloodstream.
↳ provides info about cancer mutations & treatment response.

7. Pharmacogenomic Biomarkers:
· Drug Metabolism Enzymes: Genetic variations affecting the metabolism of drugs, influencing individual responses to meds.

8. Immunologic Biomarkers:
· Immune cell activity: Assessment of the activity & composition of immune cells.
↳ relevant for immunotherapy & autoimmune diseases

9. NGS:
· looks for changes in an individuals DNA or tumor cells
↳ can lead to early on diagnoses + treatment plans.

· Biomarker Driven Therpies:
- When we use Biomarkers to find the best course of action for diseases
- Most commonly used in oncology.

Jan. 9, 2024

How does Precision Medicine work?

*Process varies but there are some key fundamentals.

1. Genomic analysis:
   - In precision medicine, the most vital step is to analyze the patients genetic makeup.
     - Involves sequencing the patients DNA to identify genetic variations, mutations, and/or markers that may be associated with certain diseases/conditions
2. Biomarker Identification:
   - Doctors use advanced diagnostic tests to identify specific biomarkers that help confirm a diagnosis or moniter the effectiveness of treatments.
   - PM relies on the identification of biomarkers
     - These tests include blood tests, imaging studies, or other types of diagnostic tests.
3. Disease Stratification:
   - Subtyping Diseases: PM aims to catagorize diseases into subtypes based on specific molecular characteristics.
     - Allows for more targeted & effective treatments as different subtypes react differently.
4. Tailored treatment Plans:
   - Targeted Therapies: Based on the results of the genomic analysis & precision diagnostics, once specific genetic mutations or biomarkers are identified, treatment plans can be tailored to target these specific factors.
     - ↳ These therapies may include meds, surgies, or other interventions
       - ↳ Designed to interfere with specific molecules involved in the growth of the disease.

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5. Predictive Modeling + Integration of clinical & molecular Data:
   - Predictive Analytics: PM uses advanced data analytics & computational modeling to predict how individuals are likely to respond to particular treatments
     ↳ helps guide doctors in selecting the most effective interventions.
   - Comprehensive Analysis: Precision medicine involves the combination of clinical data (patient history, symptoms, etc.) with molecular data (genomics, proteomic, metabolomic, etc.)
     ↳ helps in creating the best course of action.
6. Ongoing Monitoring:
   - Doctors will continue to monitor the patient's progress & do tests & assessments to adjust their treatment plan as needed to achieve the best possible outcomes.
     ↳ PM is not a one-time event but rather an ongoing process.

How does PM work?

Patient Stratification:

- In PM, patient stratification is a leading role as it allows for individuals to be placed in their subpopulations based on their genetic backgrounds.

Most common Groups:

1. Genetic Mutations:
   - May be stratified based on specific genetic mutations associated with their disease.
     - ex. in cancer, tumors with certain mutations may be catagoriced into distinct groups for targeted therapies.
2. Biomarker therapies:
   - Stratification based on the expression of specific biomarkers, such as proteins or other molecules is common.
     - ex. breast cancer patients may be stratified based on the expression of hormone receptors (eg. estrogen or progesterone receptors)
3. Molecular Subtypes:
   - Diseases may have different molecular subtypes based on unique molecular characteristics (espically cancer)
     Ex. Breast cancer can be divided into HER2-positive, triple-neg, or luminal based.
4. Metabolic Profiling:
   - Metabolomic data, which involves studying the small molecules involved in cellular processes, can be used to catagorize patients into different groups with varied responses to treatments.

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5. Immune System Characteristics:
   - Can be stratified based on the characteristics of their immune system.
   - Could involve assessing the presence/absence of specific immune markers that influence responses to immunotherapeutic interventions.
6. Response to Previous treatments:
   - Stratified based on their responses to previous treatments.
     ↳ helps identify which subgroups are more likely to respond to certain therapies.
       ↳ Guides future decisions.
7. Disease Stage:
   - Based on the severity of the disease is a common approach.
     ↳ helps tailor treatments to the specific needs of patients at different stages.
       ↳ optimizing the likelihood of success.
8. Genomic Profiling:
   - Whole-genome or whole-exome sequencing can reveal a comprehensive genomic profile of a patient's disease.
     ↳ This can guide treatment decisions.
9. Risk factors & predispositions:
   - Assessing patients for specific risk factors or predisp-ositions that influence disease development.
     ↳ allows for personalized preventive strategies & early interventions.
10. Epigenetic Modifications:
    - Epigentic changes (eg. DNA methylation) can influence gene expression.
    - stratification based on epigenetic profiles may reveal subgroups with distinct treatment responses.

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Jan. 10, 2024

- Stratification is crucial as it allows different individuals to fit into a specific category tailored for them rather than being placed in one large category where they may not receive the most vital treatment for them.

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Cancer & Tumors

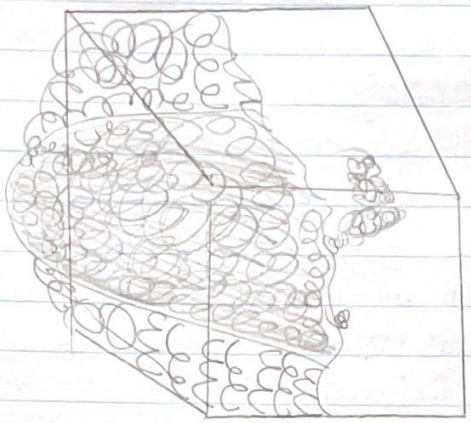
- What is it?
  - Cancer is a disease in which some of the body's cells grow uncontrollably & continue to spread to other regions in the body.
    - May start almost anywhere in the body.
- How does it work / how it spreads?

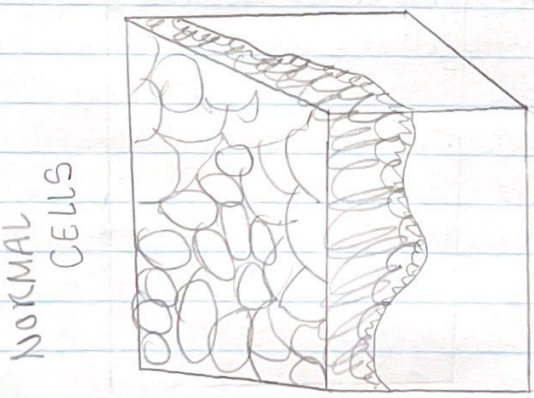
cell division {
- Normally, human cells grow & multiply to form new cells as the body needs them.
  * When cells grow old or become damaged, they die, and new cells take their place.
- However, sometimes this orderly process breaks down, & abnormal or damaged cells grow & multiply when they shouldn't. These cells may form <u>tumors</u>.
- Cancerous tumors spread into, or invade, nearby tissues & can travel to distant places in the body to form new tumors; called <u>Metastasis</u>.

- Most people who die as a result of cancer die due to metastatic disease. Sometimes, taking treatment may help expand the lifespan of a person but in other cases, the main goal to control metastatic cancer, is to take control of the development & growth of the cancer or manage & help ease the pain.
- It is important to get metastatic cancer treated as it causes damage to the way the body functions

Jan. 13, 2024

How does cancer form?





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Types of genes that cause cancer

- Cancer affects 3 main types of genes:
  - Proto-oncogenes:
    - In the body, the proto-oncogenes have the role of growth & division
    - Sometimes, when proto-oncogenes are altered or become hyper-active, they morph into genes that can cause cancer, or oncogenes
      - This allows cells to grow more & survive when they shouldn't.
  - Tumor Suppressor Genes:
    - Also take part in controlling cell division & growth
    - If some of the cells are altered it will lead to them dividing uncontrollably.
  - DNA Repair Genes:
    - The genes fix damaged DNA
      - ↳ Are vital
    - If cells have any mutations in these genes, usually the cells start developing other mutations.
      - When this happens, it could lead to the mutations causing changes in the person's chromosomes.
        - ex. some chromosomes could multiply & some parts can be deleted altogether.
        - The combo of all the mutations may make some cells cancerous as a result.

** Scientists have researched molecular changes that cause cancer & have created a treatment that targets these mutations. Additionally, they have also found a pattern of certain mutations that are most commonly found in cancers.

January. 16
2024

Pros vs. Cons

Pros:

- Empowering the prevention medicine:
  - Shift the emphasis in medicine from reaction to prevention
  - Predict susceptibility to disease
  - Improve disease detection
  - Preempt disease progression
  - Customize disease-prevention stratagies
- Increased Efficiency:
  - Precision medicine works to increase the efficiancy of medical treatment.
    - By identifying the most effective treatment for each patient, doctors can avoid using ineffective or unnecessary treatments
  - Prescribe more effective drugs
- Improved patient outcomes:
  - As patients have treatments tailored to them, there is a better chance they will react positively rather than using a general treatment which may not be suitable for them.
  - Avoid prescribing drugs with predictable side effects.
- Enhanced patient experience:
  - Precision medicine enhances the patient experience by providing tailored treatments which can improve quality of life & reduce side affects.
- Reduced healthcare costs:
  - Reduce the time, cost, & failure rates of pharmaceutical clinical trials
  - Improving patient outcomes & the efficancy of medical treatments
  - Reduced healthcare costs in the long run
  - Eliminate trial & error inefficiencies that inflate costs & undermine patient care.

Jan. 16, 2024

CONS:

- Limited availability / accessibility:
  - PM is still in its early stages of development & implementation.
    - Cannot be something used in a remote situation.

- Ethical & Privacy Concerns:
  - huge concern, as PM relies heavily on genetic data and personal info to function, raising concerns about privacy & potential misuse.
    - Protecting this data from unauthorized access & ensuring ethical practices in its usage.

- Complex Regulatory landscape:
  - Presents unique regulatory challanges, due to the concept of personalized treatments, which may involve the growth of new drugs or diagnostic tools.
    - ↳ Requires flexible regulations to support innovation
    - ↳ May be a lengthy & complex process, slowing down the implementation of PM.

- Expensive / Time-consuming:
  - Implementing PM involves various processes (eg. genetic testing, data analysis, & treatment customization) which come with a hefty cost & may be extremely time consuming.

Jan. 17, 2024

Effectiveness / success rates

Background info:

- Matched cohort study of 72 patients
  - Metastatic cancer of diverse subtypes in the setting of a large, integrated healthcare delivery system.
- Analyzed outcomes of 36 patients who got genomic testing & targeted therapies (Precision med)

vs.

- 36 historical control patients who got standard chemo (Traditional med)
- Study was conducted between July. 1, 2013 - January 31, 2015.

Results:

- Average progression-free survival was 22.9 weeks for the PM group & 12.0 weeks for the control group.
- Per patient charges per week were $4,665 in the PM group & $5,000 in the control group.

Genomic analysis included NGS-based oligoselective exon sequencing of 96 cancer related genes.

Conclusion:

" These findings suggest that Precision Cancer Medicine may improve survival for patients with refractory cancer without increasing healthcare costs. Although the results of this study warrant further validation, this precision medicine approach may be a viable option for patients with advanced cancer."

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Graphs on next pg. →

Pg. 20

Jan. 17, 2024

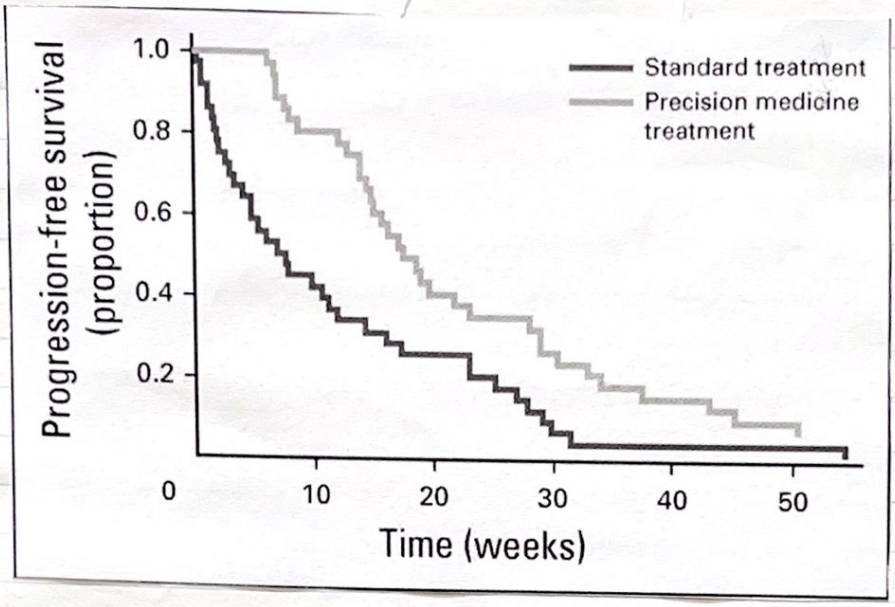

Table 2. Health Care–Associated Cost Outcomes

Cost Outcome	Patients Who Received Precision Medicine		Control Patients		
	Mean ($)	SD ($)	Mean ($)	SD ($)	*P*
Total costs per patient	91,790	85,070	40,782	42,267	.002
Total drug costs per patient	59,259	51,425	20,189	34,299	< .001
Cost per patient per progression-free survival week	4,665	3,041	5,000	6,509	.126

Abbreviation: SD, standard deviation.

Jan. 18, 2024

COST

- Cost varies depending on the case & the individual.
  ex. depending on a certain region's healthcare infrastructure and/or insurance coverage, the cost will differentiate.
- The PM therapies that a patient may be prescribed, based on the results of their genomic sequencing, can carry hefty prices too. Often more than $10,000 a month.

- PM is not a one-time thing and this often makes prices skyrocket.
  ↳ PM is something that requires continues monitoring.
  ↳ Patients with lower end salaries and/or insurance may not be able to use PM & will have to opt for traditional treatments.
  ↳ This may not be suitable for their health

- As PM requires a large period of time the total cost may come out to be of $250 000 or more
- The cost for precision medicine generally rises as more genetic profiling is required and the case of your illness.
- Often Precision oncology cases are the most expensive as it includes all the general costs of cancer treatment along with the expenses of precision medicine

January. 18, 2024

Precision Oncology

- Precision oncology is a rapidly evolving approach to cancer treatments that involve customizing therapies based on the individual characteristics of each patient & their tumor.
  - ↳ Allows for a more targeted & effective approach to cancer care
  - ↳ Same concept as general PM

- A reason as to why precision oncology is more effective than traditional cancer treatments is Disease Heterogenity.
  - Traditional cancer treatments are effective in only a subset of the patient population due to disease heterogenity.
  - Tumors can have different underlying genetic causes & may express different proteins, leading to variable responses to generic treatments.
    - ↳ Precision oncology avoids this by tailoring therapy selection to each patient based on their specific genetic & molecular characteristics.

January 19, 2024

Types of oncology treatments
CAR T-cell therapy

What is it:

- It is equivalent to giving a patient "a living drug"
- The backbone of CAR T-cell Therapy is T-cells
  - T-Cells help orchestrate the immune response & directly kill cells infected by pathogens
- As of the moment, CAR T-cells therapies are individually customized for each patient, thus relating it with precision medicine
- Most commonly used in leukemia and lymphoma

How does it work:

- CAR T-cells therapies function by collecting T-cells from the patient & then re-engineering them in the lab to produce proteins in their surface called chimeric antigen receptors (CARs).
  - The CARS recognize & bind to specific proteins &/or antigens on the surface of cancer cells & kill them

Detailed Steps:

- 1. Patient T-cells are removed from their blood
- 2. The gene for CARs is inserted into the T-cells in a lab setting.
  - ↳ The gene encodes the engineered CAR proteins that are expressed on the surface of the patients T-cell, creating CAR-T-cells.
- 3. Millions of CAR T cells are grown
- 4. Given to the patient through intravenous infusion
- 5. CAR T-cells bind to the antigens on the cancer cells & kill them

- If all goes as planned, the CAR T-cells will continue to multiply in the patient's body & with guidance from their engineered receptor (synthetic molecules), recognize & kill any cancer cells that harbor the target antigen on their surfaces.

Making a CAR T-Cell:
- Each CAR bridges the cell membrane
- Part of the receptor is located outside the cell and part within the cell.
  - The part of the CAR that extends out from the cell's surface is usually composed of fragments, or domains, of lab-made antibodies.
- Which domain are used, affects how well the receptor recognizes or binds to the antigen on tumor cells.
  - The internal part of each CAR has signaling & "co-stimulatory" domains.
    - ↳ These transmit signals into the cell after the receptor interacts with an antigen.
      - The different domains that are used can affect the cells' overall function.

- The CAR T-Cell therapies approved by the FDA so far target one of two antigens on B cells, CD19 or BCMA.

Diagram →

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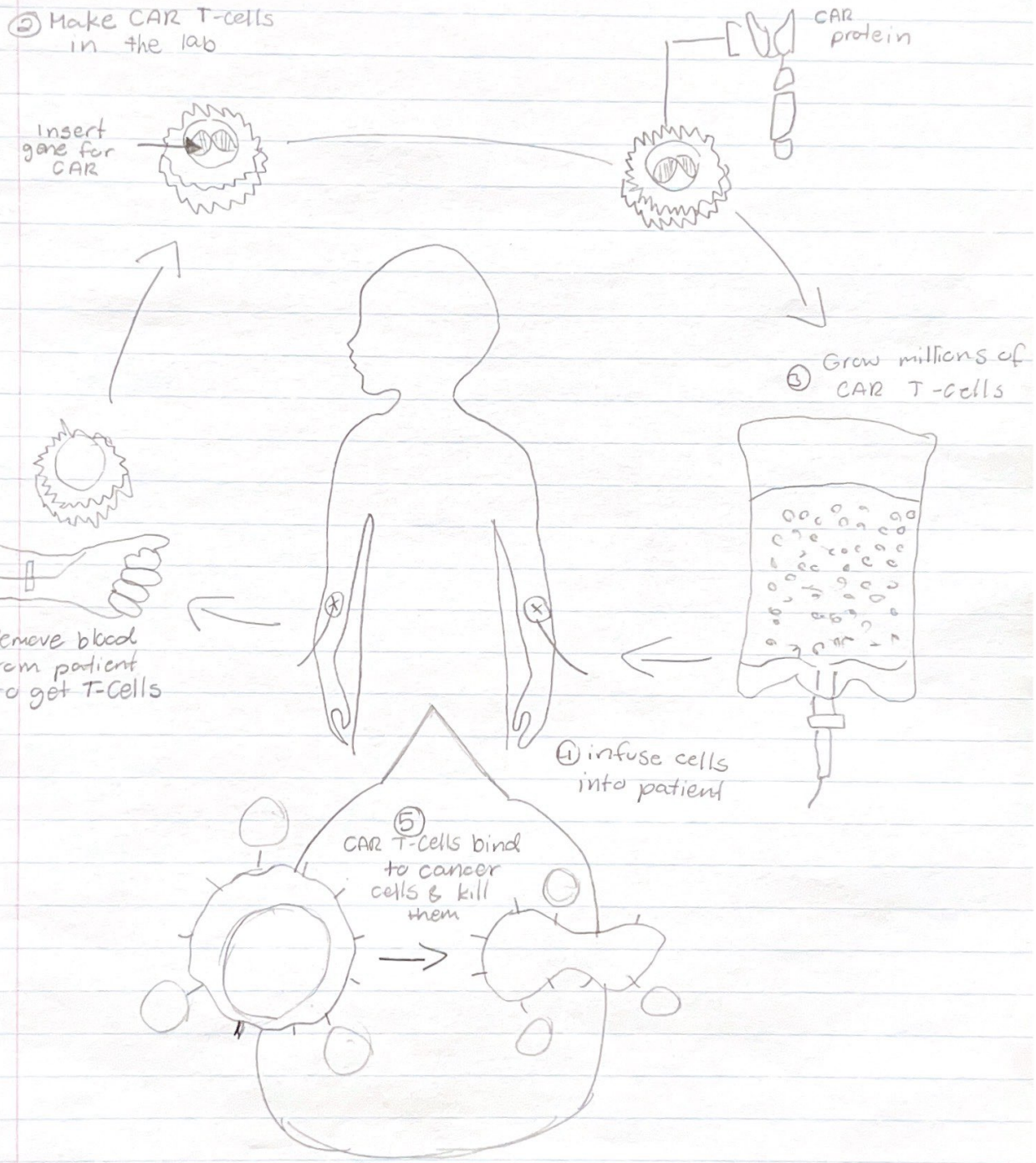
Jan. 20, 2024


② Make CAR T-cells in the lab
Insert gene for CAR
CAR protein
③ Grow millions of CAR T-cells
① Remove blood from patient to get T-cells
④ infuse cells into patient
⑤ CAR T-cells bind to cancer cells & kill them

Jan. 21, 2024

Tumor Infiltrating Lymphocyte

What is it & How does it work?

- TILs are an experimental cell therapy being developed for treating solid tumors.

- Lymphocytes, or white blood cells, are an important part of the immune system that help the body fight off infections or eliminate diseased cells.
- Lymphocytes are composed of T cells & B cells
- Lymphocytes are constantly patrolling the body to identify cells that shouldn't be present (including cancer)
  - ↳ As cancers grow, lymphocytes recognize these cells as abnormal & penetrate into the tumor.
    - ↳ These are TILs.
- Once in the Tumor, the TILs begin working to kill cancer cells
  - Sometimes, they're prevented from doing that by brakes in the immune system or signals from the tumor that weaken the immune response.
    - ↳ Immune checkpoint inhibitors were developed to block some of those brakes & unleash the immune cells to attack cancer.

How can these cells be used for cancer therapy?

- As TILs come directly from the tumor, they already recognize many targets on the cancer cells.
  - ↳ This is an advantage as it prevents the tumor from evading our efforts by hiding one target at a time.

- To use TILs as a therapy, we must help them overcome the hurdles in the tumor environment & effectively eliminate the cancer. We can do this in two ways:

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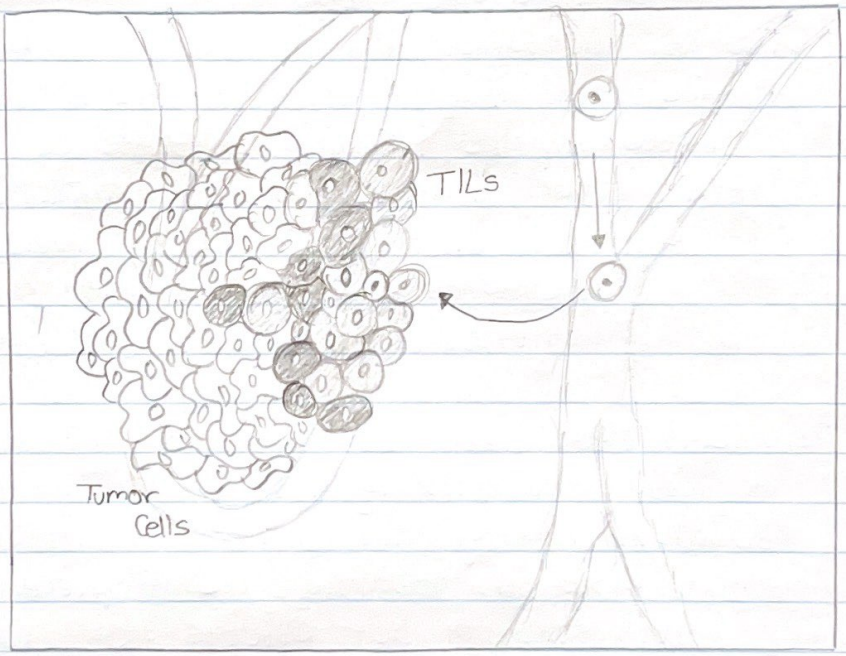
- Expanding the TILs
- Engineering them with certain attributes

- By expanding the TILs, we can give the patient a much larger army of immune cells that are already trained to recognize & attack the patient's specific tumor.
- Engineering TILs enhances their ability to fight cancer cells.
  - ↳ ex. we can genetically engineer TILs to be resistant to signals coming from the tumor that normally turn off the T-cells.



CONCLUSION

- PM tailors treatment to individual characteristics
  - ↳ Genetics, environment, lifestyle
- Relies on DNA sequencing & omics tech for personalized treatment.
- Successful in cancer by targeting specific mutations, improving outcomes
- Immunotherapy breakthroughs showcase its potential
  - ↳ CAR T-cells & TILs
- Ethical concerns include privacy, informed consent, & misuse prevention.
- Ethical frameworks & privacy safeguards needed before full implementation.
- Challanges include cost, but potential for long-term efficiancy
- Promises reduced treatment costs, & avoids trial & error.
- Potential to optimize care & improve outcomes
- The challanges are being addresed through tech advancements / regulations.
- PM is expected to benefit patients worldwide
- Continued advancement & adoption is expected to lead to better outcomes.