Molecules to Medicine
Course Goals

Goals

1. Explain how the normal human cell is constructed and how it functions.
2. Describe the basic principles of DNA structure, synthesis and repair.
3. Describe RNA structure, major types of RNA and their function, synthesis of mRNA, and mechanisms of gene regulation.
4. Discuss amino acids, protein primary, secondary, tertiary, and quaternary structure, and principles of translation and translational control, and basic principles of enzyme function and kinetics, and mechanisms of protein degradation.
5. Comprehend the basic principles of human inheritance, the molecular basis of inherited disease, and methods to search for human disease genes.
6. Comprehend the basic principles of imprinting, cytogenetics, preparing and interpreting a pedigree, genetic regulation of sex determination, and describe the major forms of inherited disease encountered clinically.
7. Describe and discuss the major structural compartments, organelles, and cytoskeletal components in the cell and their function.
8. Explain the basic principles of intracellular trafficking, and intracellular signaling.
9. Provide a basic understanding of membrane structure and function, and basic principles of cell physiology, including cell composition and volume regulation, membrane potential, gated channels, and action potentials.
10. Describe how the cells in the body form major types of functional tissue, including epithelium, connective tissue, and muscle, and describe normal histology of human tissues.
11. Describe the underlying molecular and cellular perturbations of certain human diseases and how these human diseases present clinically.
12. Understand the basic principles of bioenergetics that govern catabolic and metabolic reactions that occur within cells.
14. Understand how the cell cycle is orchestrated and regulated through actions of specific cyclins, cyclin-dependent kinases, inhibitors of kinases, checkpoints, and how acquired or inherited alterations of cell cycle regulation lead to cancer.
15. Understand basic mechanism of programmed cell death, including apoptosis and autophagy.
16. Explain how human genetic variation relates to measured phenotypic variation in health, disease, and differential response to medications.
17. Understand and apply genetic counseling and related ethical practices in clinical genetic situations.
Acids, Bases and Buffers

1. Describe the law of mass action.
3. Write the Henderson-Hasselbalch (H-H) equation for any given weak acid or base.
4. Define the H-H equation for the bicarbonate buffer system in extracellular fluid and use it to evaluate clinical lab data.
5. Define normal blood pH, [HCO3⁻] and pCO₂.
6. Describe how weak acids and bases work to buffer pH and define the pH range of maximal buffering capacity.
7. Use the H-H equation to solve problems of how pH changes in defined buffers, i.e., determine how many equivalents of acid or base are needed to titrate the ionizable groups(s) of a weak acid or base from a starting pH to a final pH, given its concentration and pKa.

Action Potential I

1. Define the threshold for an action potential.
2. Explain what an action potential is and understand that it is important for neural signaling.
3. Understand how the activation and inactivation gates of sodium channels are affected by changes in the membrane potential.
4. Understand how the activation gates of potassium channels are affected by changes in the membrane potential.
5. Understand how the action of voltage-gated sodium and potassium channels generates the action potential.
6. Understand the causes of the membrane’s refractory period.
7. Understand how neurons accommodate to slow depolarization.
8. Understand how few ions cross the membrane during the action potential, and relate this to maximum rate at which cells can produce action potentials.

Action Potential II

1. Explain why action potentials are necessary for rapid communication over long distances.
2. Identify the “safety factor” for conduction, and explain how this supports AP conduction along branching axons, and enables the axon to generate action potentials at a higher rate.
3. Describe the role of refractoriness in preventing action potentials from reversing direction, and propagating “backwards”.
4. Explain how action potential diameter affects conduction velocity and threshold for extracellular excitation.
5. Explain how myelin sheathing supports AP conduction.
Alzheimer Vignette
1. Comprehend the pathophysiology of Alzheimer's Disease.
2. Describe the central role of post-translational amyloid precursor protein processing in the pathogenesis of Alzheimer's Disease.
3. Consider interventions that might help delay onset or prevent the development of Alzheimer's Disease.

Amino Acids, Peptides and Proteins I
1. Identify α carbon, the NH₂, COOH, and side chains (R groups) of an amino acid.
2. Distinguish between amino acids with hydrophobic, polar, acidic and basic side chains.
3. Describe the function of disulfide bonds within proteins.
4. Describe the major post-translation covalent modifications of amino acid side chains in proteins. Identify the post-translational modification targeted by the disease process or medicine discussed in class.
5. Distinguish three covalent bonds including the peptide bonds that make the backbone of a polypeptide chain.
6. Distinguish that the amino acid sequence determines the function; mutations in amino acid sequence can cause genetic disease.
7. Recognize that proteases and the specific breaking of peptide bonds can have important functions.

Amino Acids, Peptides and Proteins II
1. Describe hydrogen bonds and their role in secondary structure formation.
2. Describe the two most common protein secondary structures.
3. Explain tertiary and quaternary structures.
4. Explain the role of loops in protein structure and function.
5. Explain how to use Kd to represent binding strength.
6. Explain how binding specificity can be achieved.
7. Explain how heme enables myoglobin to bind oxygen.
8. Explain the molecular basis of carbon monoxide poisoning.
9. Explain why hemoglobin is a good oxygen transporter.

Amino Acids, Peptides and Proteins III
1. Identify the factors that cause protein denaturation.
2. Describe the most fundamental conclusion drawn from the Ribonuclease refolding experiment.
3. Describe the two classes of chaperones and the general function of chaperones.
4. Explain why sometimes protein disulfide isomerase or protein prolyl isomerases are required for protein folding.
5. Recognize that protein mis-folding is the major cause of prion disease, Alzheimer's disease, and Parkinson's disease.
6. Identify the secondary structure changes and the infectious agent in prion disease.
7. Describe the major approaches for purifying a protein.
Androgen Receptors Clinical Vignette

1. Identify the sources of androgen in the body relevant to prostate cancer.
2. Describe the structure and function of the androgen receptor in prostate cancer.
3. Describe the mechanisms of resistance to traditional endocrine therapy for prostate cancer, describing enzalutamide and abiraterone’s effect on these mechanisms.

Apoptosis

1. Describe characteristic plasma membrane, cytoplasmic, and nuclear events of apoptosis.
2. Compare and contrast apoptosis and necrosis in terms of morphology, typical triggers of the two phenomena, and relative importance in physiological and pathological processes.
3. Name tissues in which there is most and least apoptosis. Suggest reasons for this difference.
4. Describe the role of caspases in apoptosis, and discuss the role that the mitochondrion may play in the process. Identify the roles of Caspases 8, 9, and 3.
5. Distinguish between the signaling of the intrinsic and extrinsic apoptosis pathways.
6. Discuss the essential biological difference between phagocytosis of apoptotic and necrotic cells.
7. Discuss the importance of apoptosis in tumor formation and progression.
8. Describe a mechanism by which one cell can induce apoptosis in another cell, and give an example.

Autophagy

1. Differentiate between two main types of autophagy: macroautophagy and chaperone-mediated autophagy.
2. Describe the process of macroautophagy.
3. Describe the rationale behind autophagy’s protective action against neurodegeneration.
4. Identify mechanisms by which apoptosis induction and autophagy are connected.

Autosomal Dominant Disorders

1. Recognize the characteristic pattern in a pedigree showing autosomal dominant inheritance.
2. Describe features that may complicate the assessment of an autosomal dominant pedigree.
3. Recognize concepts in dominant inheritance including penetrance, expressivity, locus heterogeneity and paternal age effect.
4. Recognize and describe the clinical features and molecular basis of Achondroplasia, Neurofibromatosis Type 1, OSteogenesis Imperfecta and Tuberous Sclerosis.
5. Describe unique features of Trinucleotide-Repeat disorders.
6. Recognize and describe clinical features and the molecular basis of Huntington Disease.
Autosomal Recessive Disorders

1. Describe the common characteristics of disorders that are of autosomal recessive inheritance.

2. Calculate allele frequency and carrier frequency of a given autosomal recessive disease when provided with the disease frequency, and vice versa.

3. Describe the following concepts: 1) Allelic heterogeneity 2) Compound heterozygote 3) Parental consanguinity 4) High-risk groups

4. Describe Phenylketonuria (PKU).

5. Discuss biochemical deficiencies in PKU patients and the appropriate treatments.


7. Describe newborn screening procedures for PKU and importance of the timing of the test.

8. Describe alpha 1-Antitrypsin Deficiency (ATD).

9. Recognize clinical features of alpha 1-antitrypsin deficiency and the influence of environmental factors on the expression and severity of the disease (ecogenetics).

10. Identify which enzyme is the primary target of alpha 1-antitrypsin.

11. Identify the two most common mutant alleles that cause ATD and the severity of different allelic combinations, and describe why some ATD patients have liver failure.

12. Describe Tay-Sach Disease (T-S).

13. Explain biochemical defects in Tay-Sachs disease and why the brain is the major target.


15. Describe the high-risk group for Tay-Sachs disease and the available methods for carrier screening and prenatal screening in the high-risk population.
Bioenergetics

1. Define:
   a) Entropy
   b) Enthalpy
   c) Free energy
   d) High energy compounds
   e) Oxidation-reduction reaction

2. Discuss the first and second laws of thermodynamics

3. Describe the different forms of energy.

4. Apply the following basic thermodynamic equations that describe the relationship between free energy, the equilibrium constant, enthalpy and entropy and calculate one unknown variable in an equation when all other variables are given.
   a) \( \Delta G = \Delta G_0 + RT \ln \frac{\text{PRODUCTS}}{\text{REACTANTS}} \)
   b) \( \Delta G_0 = -RT \ln K_{\text{eq}} \)
   c) \( \Delta G = \Delta H - T \Delta S \)

5. Describe the relationship between the sign of the standard free energy and the direction of a reaction under standard conditions.

6. Describe the effect of positive/negative entropy or enthalpy on the thermodynamic forces driving a reaction based on the equation: \( \Delta G = \Delta H - T \Delta S \).

7. Calculate the numerical conversion between free energy (\( \Delta G \)) and Redox potential (\( \Delta E \)) in biological systems. \( \Delta G = -nF\Delta E \)

8. Recognize the fact that series of electron transfer in biological system can generate energy.

9. Recognize the fact that the standard free energy changes for a set of reactions are additive, therefore reactions with positive and negative free energy changes can be coupled.

10. Describe the major "high-energy" compounds used in biological systems and the principle of energy storage in "high-energy" bond.

Calcium Signaling

1. Describe the functions of cytoplasmic Ca2+ ion buffers and how these buffers affect cytoplasmic Ca2+ signals.

2. Describe the routes by which extracellular Ca2+ enters the cytoplasm, the routes by which Ca2+ moves out of the ER/SR into the cytoplasm, and the routes by which Ca2+ is extruded from the cytoplasm (a) into the extracellular space and (b) into the lumen of the ER/SR.

3. Describe EF hands and C2 domains, identify the archetypical protein that contains EF hands and the archetypical protein that contains a C2 domain, and determine whether these domains are present in other proteins.
Case Studies in Genetics

1. Explain and contrast the molecular genetic features and mechanisms of three key genetic diseases: Achondroplasia, Nonsyndromic deafness, Fragile X syndrome, Marfan syndrome, Rett syndrome, and Xeroderma Pigmentosum.


4. Discuss the following two scenarios: 1) the use of genetic testing for couples at risk for a deaf child to reduce the risk of them having a child with congenital deafness, and 2) two deaf parents that use testing to ensure they have a child who is also deaf.

Cell Composition and Volume Regulation

1. Recite typical values for the volumes of extracellular fluid (ECF; about 14 liters; 1/3 of total body fluid), intracellular fluid (ICF; about 28 liters; 2/3 total body fluid), and plasma (2.8 liters, 20% of ECF) compartments.

2. Describe the major differences in ionic composition between ECF and ICF.

3. Describe the two most important functional properties of membranes, one conveyed by lipids, the other by channels and transporters.

4. Recite the routes by which a given substance can traverse a membrane.

5. Determine which direction an uncharged substance will move across a membrane, given its concentrations on the two sides.

6. Determine under a given set of conditions, whether a cell will swell or shrink.

7. List the three mechanisms that different cells have evolved to keep from swelling and bursting.

8. Describe which direction water will move across a semi‐permeable membrane, given the solute compositions of the fluids on either side of the membrane.

9. Describe the difference between diffusion and osmosis.

10. Describe which substance must move into or out of a cell in order for the cell's volume to change.

11. Describe the effect of having a membrane with different, non-zero permeabilities (i.e., reflection coefficients less than 1) to different solutes.

12. Define molarity, osmolarity, equivalents, and tonicity, and describe how to convert between them.

Cell Signaling

1. Describe principle types of detectors of extracellular signaling molecules.

2. List other "tools" of signaling pathways, including at least three 2nd messengers.

3. Describe at least three mechanisms for signal termination (including phosphodiesterases).

4. Evaluate a "pathway" for amplification and termination.

5. Identify "nodes" (such as calcium) and "modules" in a signaling pathway, and evaluate the potential for crosstalk in signal transduction as measured by the ability to construct detailed annotated drawings and by criterion-based testing.
Chromosomal Anomalies I
1. Describe the events in meiosis that produce genetic variability among offspring.
2. Compare and contrast mitotic and meiotic cell divisions.
3. Define and interpret the karyotypic designations used in cytogenetic reports to describe numerical abnormalities.

Chromosomal Anomalies II
1. Describe the mechanism(s) of common chromosomal structural rearrangements.
2. Define the differences between balanced and unbalanced structural rearrangements.
3. Assess the risks in families that are carriers of balanced translocations to have unbalanced progeny.
4. Identify the most common contiguous gene syndrome in humans (this will be discussed again in the Molecular Cytogenetics lecture, November 3rd, 8am).

Chromosomal Anomalies III: Genomic Imprinting
1. Describe the concept of imprinting and methylation.
2. Name which main chromosomes have imprinted regions.
3. Recognize common genetic disorders associated with imprinting.

Cilia
1. Identify the components of cilia.
2. Explain how cilia are assembled.
3. Explain the differences between motile and sensory cilia.
4. Identify signaling pathways that function through cilia and explain why cilia are used for signaling.
5. Provide examples of how cilia function in development and tissue homeostasis.
6. Recognize the clinical features and cilia defects associated with ciliopathies.

Connective Tissues I
1. Describe the structural relationships among connective tissue and epithelia, blood vessels, and muscles.
2. Describe connective tissue cellular and extracellular components and their functions: State the types, origins, and functions of the different cell types found within connective tissues. Describe the components of the extracellular matrix, their functions, and how they are organized in different connective tissues.
3. For the proteins that form extracellular fibers, describe their types, their properties, and how they are made and assembled in the extracellular matrix.
4. Describe the basis and functional consequences of connective tissue diversity.
5. Describe how connective tissues are regulated upon tissue injury. Describe the events that occur following wounding and inflammation.
Connective Tissues II
1. For cartilage, describe its cellular and extracellular composition, its structural properties, and how it is organized. State the functions of cartilage tissue.
2. Describe how cartilage grows during fetal and child development.
3. State the characteristics that distinguish the three basic types of cartilage.
4. State the different cell types found in bone. For each cell type, describe their functions, their origins, and describe how they are organized in bone tissue.
5. Describe the composition of bone extracellular matrix, and the functions of the different components discussed in class and lecture notes. Describe where these extracellular matrix components are made, and how they are deposited to form bone matrix.

Connective Tissues III
1. Describe the two different processes that lead to bone formation. Describe how long bones grow in length and in width.
2. Describe the sequence of events that occur in bone remodeling.
3. Describe how bone formation and remodeling is regulated.
4. Describe how defects in bone remodeling leads to disease.
5. Describe how calcium is deposited and resorbed from bone matrix, and how regulation of bone cells controls the levels of blood calcium.

Control of Gene Expression I
1. Discuss the basics of eukaryotic transcription (DNA control elements, transcription factors) and the role they play in human disease and list the different eukaryotic DNA control elements.
2. Define promoter proximal element and enhancer.
3. Describe a disease that arises from a mutation in a DNA control element, and how the mutation leads to the disease state.
4. Describe the role of transcriptional activators and repressors.
5. List the two classes of activators and repressors.
6. Describe the domains of a sequence specific DNA binding protein.
7. List the four major families of sequence specific DNA binding proteins and describe the means for categorizing the proteins into these families.
8. Describe a particular human disorder that arises from a mutation in a sequence specific DNA binding protein, explaining how the mutation leads to the disorder.
9. Describe combinatorial control as a mechanism for controlling gene expression.
Control of Gene Expression II

1. Describe how chromatin structure affects transcriptional control and list the two classes of chromatin remodeling factors and briefly describe how they work.

2. Define HATs and HDACs and describe how their activity influences transcription.

3. Give an example of a disease in which histone acetylation is altered, and describe the defect that leads to altered histone acetylation.

4. Describe how activators/repressors modulate transcription via their interaction with general transcriptional machinery vs. with chromatin.

5. Discuss the basic principles of transcriptional regulation including how specificity is achieved and how protein-DNA interactions contribute to transcriptional control.

Control of Gene Expression III

1. Describe how sequence specific DNA binding proteins are themselves regulated, and how their dysregulation may lead to human disease and list at least four mechanisms by which sequence specific DNA binding proteins are regulated.

2. Describe how the activity of nuclear hormone receptors is controlled, and how tamoxifen acts in breast cancer therapy.

3. Give an example of a sequence specific DNA binding protein regulated by nuclear entry and describe the mechanism by which its entry is controlled.

4. Describe how the amount of an activator/repressor can be regulated within the cell.

5. Describe a mechanism by which the DNA binding activity of a sequence specific DNA binding protein can be inhibited.

6. List a protein modification that can alter the activity of a sequence specific DNA binding protein, and explain the mechanism by which the activity is altered.

7. Aside from transcriptional regulation, list at least 3 additional mechanisms to control levels of gene expression.

Crohn's Disease Vignette

1. Employ listening and empathy in actively listening to patients' symptoms and not dismissing them as "stress-related".

2. Appreciate why patients with IBD experience feelings of shame and embarrassment related to their symptoms and their disease.

3. Describe how the activation of IBD during puberty can impact patients' emotional and social development.

4. Formulate a medical history of IBD patients that extends beyond merely asking them about frequency and quality of their bowel movements.

5. Organize a discussion about proceeding with an ostomy surgery for a patient with IBD that incorporates the patient's own perspective and values in the patient-physician conversation.

6. Correctly diagnose clinical presentations of inflammatory disease.

Cystic Fibrosis Vignette

1. Describe the genetics and underlying protein defect in Cystic Fibrosis (CF).

2. Describe current understanding of pathophysiology underlying CF lung disease.

3. Describe the diagnostic and therapeutic approaches in CF.
Cytoskeleton I

1. Discuss the concept of a cytoskeleton.
2. Describe microtubule and intermediate filament cytoskeleton (their properties, their functional roles, and their protein composition).
3. Discuss cytoskeletal dynamics and the role of certain proteins and drugs in tubulin polymerization/depolymerization.
4. Explain the concept of molecular motor. Explain the mechanisms of tubulin-based movement and intracellular transport.
5. Discuss the role of microtubules in mitosis.
6. Discuss the cytoskeleton in the context of disease processes.

Cytoskeleton II: Actin & Cell Motility

1. Describe the three types of cytoskeletal elements, their properties, their functional roles, and their protein composition.
2. Discuss cytoskeletal dynamics and the role of certain proteins in actin filament formation, polymerization/depolymerization.
3. Describe the role of actin cytoskeleton in epithelial cell polarity and discuss some diseases associated with that.
4. Explain the concept of molecular motion, and the mechanism of actin-based organelle movement and muscle contraction.
5. Discuss the concept and the key steps of cell movement.
6. Discuss cell motility in the context of developmental and disease processes.
7. Describe the role of actomyosin ring in cell division.
8. Describe the mechanisms regulating the establishment and activation of the actomyosin ring and identify examples of asymmetric cell division.

DKA Vignette

1. Identify straightforward diabetic ketoacidosis (DKA).
2. Describe the major metabolic disturbances in DKA:
   - Elevated blood sugar (hyperglycemia)
   - Acidosis
   - Potassium derangements
   - Dehydration
3. Describe the stimulus for insulin release.
4. Describe at least three target-site actions of insulin.
5. Describe the risk for cerebral edema in DKA.
DNA I & II

1. Distinguish purines and pyrimidine bases, ribose and deoxyribose, ribo- and deoxyribo nucleosides, nucleotides, nucleoside di and triphosphates.

2. Discuss the relative solubility of the components of nucleotides and the diseases related to their insolubility.

3. Identify the chemistry in the phosphodiester linkage of DNA and RNA polynucleotide strands and discuss the reason for 5’-3’ polarity.

4. Discuss the important experiments that helped to establish DNA as the genetic material.

5. Describe the implications of Chargaff’s rules.

6. Describe the Watson-Crick three-dimensional model for DNA structure and recognize the major and minor grooves, the phosphodiester backbone, and the base pairs.

7. Describe the chemical basis for the stability of the double helix DNA in solution.

8. Distinguish between linear and circular and relaxed and supercoiled forms of DNA.

9. Describe the chemical modifications of bases in DNA including different forms of DNA damage (methylation, deamination, depurination, UV cross linking) and their significance to disease.

10. Explain the chemistry of DNA polymerization and how nucleoside analogues are used as drugs.

11. Describe how DNA melting temperature/annealing to complementary sequence is negatively affected if there is a mismatch and how this can be taken advantage of in diagnostic techniques to distinguish the presence of a particular unique sequence using a "probe" that is completely complementary to that sequence.

12. Define the major similarities and differences between DNA and RNA.


14. Explain how puromycin mimics amino-acyl tRNA to terminate translation.

DNA Repair

1. Describe the relationship between mutations, DNA repair and cancer. Give examples of heritable human diseases that are caused by defective DNA repair pathways.

2. Describe the sources and nature of damage to DNA, the type of machinery used to repair the damage, and the molecular consequences of failure in DNA repair, e.g. thymine dimers, uracil mis-incorporations, bulky chemical adducts, and double-strand breaks.

3. Explain the basic steps of mismatch repair, describing the type of damage repaired by this pathway, and understand the marking of the old strand of DNA by methylation in E. coli.

4. Describe the basic mechanisms of base excision repair, nucleotide excision repair, double-strand break repair by homologous recombination and NHEJ, and the types of lesions corrected by these DNA repair pathways.

5. Describe the mechanism that enables replication to continue in the face of DNA lesions that other repair pathways fail to remove, and know the unfortunate consequence of this process for the cell.


7. Describe the concept of DNA Damage Response (DDR) and how DDR can be targeted for cancer therapy.
DNA Replication

1. Discuss the meaning of these terms in the context of DNA Replication: "semi-conservative", "bidirectional", "Okazaki fragments", "origin", "fork".

2. Describe the functions of the following proteins during DNA replication:
   - origin recognition complex (ORC)
   - pre-replication complex (pre-RC)
   - DNA helicases
   - single-strand binding proteins
   - primase
   - DNA polymerases alpha, delta & epsilon
   - DNA ligase
   - sliding clamp
   - topoisomerase
   - telomerase
   - reverse transcriptase

3. Recognize that DNA polymerase requires an RNA primer, that DNA synthesis only occurs in the 5'-to-3' direction, and that errors during replication are corrected by the 3'-to-5' exonuclease proofreading activity of the DNA polymerase.

4. Describe the order of events that occur during, the differences between, and coordination of, DNA synthesis on the leading strand and the lagging strand.

5. Describe the "end replication problem" and the activity of telomerase.


7. Give examples of drugs that target DNA replication machinery.

Double-strand (DS) DNA Break Repair

1. Name five sources of DNA double-strand breaks.

2. Distinguish between the two mechanisms used to repair DNA double-stranded breaks.

3. Explain why defects in either of these two modes of double-strand break repair can increase cancer risk.

4. Describe three classes of proteins with distinct functions that, when mutated, lead to failure to repair DNA double-strand breaks.

Down Syndrome Vignette

1. Describe the chromosomal abnormalities associated with Down Syndrome and how to test for them.

2. Describe the physical features (Phenotype) seen in a patient with Down Syndrome.

3. Recognize the medical problems seen in patients with Down Syndrome.

4. Describe the developmental and behavioral phenotype of a patient with Down Syndrome.

EBM Case-Control Studies

1. Define the epidemiologic concept of case-fatality rate.

2. Discuss the strengths and limitations of case-control studies and the clinical questions best answered by this study type.

3. Describe characteristics of case-control studies, explain how these characteristics may result in bias, and recognize appropriate methods for minimizing these biases. Critically appraise a (observational) case-control study.

4. Explain the difference between risk and odds. Calculate an odds ratio. Explain the circumstances in which each is appropriate to use and how each is interpreted.

5. Recognize a population health perspective, including use of epidemiologic methods for outbreak investigation.
**EBM Cohort Studies & Testing Results**

1. Define epidemiologic concepts of incidence and prevalence.
2. Recognize differences in study design for cohort studies and randomized controlled trials. Discuss the strengths and limitations of each and the clinical questions best answered by each study type.
3. Define criteria for inferring causality from statistical associations including Hill criteria and apply to an example.
4. Describe characteristics of cohort studies, explain how these characteristics may result in bias, and recognize appropriate methods for minimizing these biases. Critically appraise an (observational) cohort study.
5. Define statistical measures commonly used in the medical literature, including sampling, normal distribution, mean, median, mode, variance, standard deviation, and range.
6. Recognize statistical methods commonly used in the medical literature, including t-tests, ANOVA, linear regression, survival analysis/Cox proportional hazards model, Kaplan-Meier curve. Understand how to interpret their results.

**EBM Cross-Sectional & Diagnostic Studies**

1. Define epidemiologic concept of prevalence.
2. Discuss the strengths and limitations of cross-sectional studies and the clinical questions best answered by this study type.
3. Describe characteristics of cross-sectional studies, explain how these characteristics may result in bias, and recognize appropriate methods for minimizing these biases.
4. Explain appropriate techniques for communicating numeric and other information from screening and diagnostic studies to colleagues and patients.
5. Calculate and apply common diagnostic/screening test information including sensitivity, specificity, and predictive values. Describe how predictive values are influenced by disease prevalence.

**EBM Interpreting RCT Results & Applying RCT Results to Patients**

1. Critically appraise a Randomized Control Trial (RCT).
2. Calculate and apply absolute risk. Explain the circumstances in which it is appropriate to use and how it is interpreted.
3. Calculate number needed to treat/harm (NNT/H), absolute risk reduction and relative risk reduction. Differentiate between disease-oriented outcomes and patient-oriented outcomes.
4. Describe barriers to understanding evidence and explain appropriate techniques for communicating numeric and other information to patients.
5. Identify and use summary sources, practice guidelines, pre-appraised sources, and sources of individual studies.

**EBM Online Short Video Assignment 1 & 2: Observational Studies, Screening & Diagnostic Tests**

1. Recognize differences in study design for both observational and experimental studies.
2. Explain how characteristics of observational studies may result in bias.
3. Describe characteristics of a screening test.
4. Calculate and apply common diagnostic/screening test information including sensitivity, specificity, and predictive values.
EBM Online Short Video Assignment 3: Interpreting Studies

1. Evaluate a study about therapy. Apply concepts that relate to validity of RCTs including randomization, concealed allocation, intention-to-treat, and blinding.

EBM Randomized Controlled Trials & Testing RCT Results

1. Differentiate between random error and bias and how these can be minimized. Define validity.
2. Describe characteristics of randomized controlled trials (RCTs) such as randomization, blinding, allocation concealment, intention-to-treat analysis (as compared with per-protocol or as-treated analyses), and follow up, and explain how these characteristics reduce bias.
3. Calculate and apply a risk ratio (also known as relative risk). Explain the circumstances in which it is appropriate to use and how it is interpreted.
4. Explain the difference between statistical significance and clinical significance. Understand type 1 and type II errors, null hypotheses, alpha level, power, p-values and confidence intervals. Accurately interpret p-values and confidence intervals in a clinical context.
5. Recognize chi-square tests. Understand how to interpret their results.

EBM Small Group: Interpreting Studies, Applying Results to Patients

1. Define criteria for inferring causality from statistical associations including Hill criteria and apply to an example.
2. Calculate number needed to treat/harm (NNT/H). Explain how it can be used to communicate risk to patients.
3. Describe barriers to understanding evidence and explain appropriate techniques for communicating numeric and other information to colleagues and patients.
4. Explain the difference between statistical significance and clinical significance. Understand p-values and confidence intervals. Accurately interpret p-values and confidence intervals in a clinical context.
5. Recognize statistical methods commonly used in the medical literature, including t-tests and chi-square tests, correlation, ANOVA, logistic regression, linear regression, survival analysis/Cox proportional hazards model, Kaplan-Meier curve, forest plot. Understand how to interpret their results.
6. Evaluate a cohort study. Apply concepts that relate to validity of cohort studies, including selection bias, selection of comparison group, exposure measurement, confounding, and loss to follow-up. Explain its relevance to patient care and clinical decision-making.

EBM Systematic Reviews & Meta-Analysis

1. Describe the evidence hierarchy. Recognize differences in study design for both observational and experimental studies including case studies; case series; cohort, case-control, and cross-sectional studies; randomized controlled trials; and systematic reviews, narrative reviews, and meta-analyses. Discuss the strengths and limitations of each and the clinical questions best answered by each study type.
2. Distinguish between narrative review articles, systematic reviews, and meta-analysis and understand issues in using them such as publication bias, forest plots, and heterogeneity.
3. Describe characteristics of a good clinical practice guideline, including a focus on clinical outcomes, use of best available evidence, and involvement of multi-professional groups and consumers in development.
EBM: Overview of Evidence-Based Medicine

1. Explain the value of evidence over opinion in making medical decisions and in the practice of life-long learning.

2. Define evidence-based medicine (EBM). Explain the EBM cycle of asking clinical questions, using appropriate resources to select high quality evidence, and applying evidence to individual patients.

3. Describe the evidence hierarchy.

Endocytosis and Protein Degradation

1. Describe two major routes for small volume endocytosis. How are these endocytic pathways related to viral infections and to bacterial ingestion by the macrophage?

2. Explain how quality control of protein synthesis ensured in the ER.

3. Describe two types of molecular chaperones.

4. Describe the proteasome, protein degradation, and the role of ubiquitin.

5. Describe the functions of the lysosome. What storage diseases occur due to mutations in lysosomal proteins such as degradative enzymes and transporters?

Enzyme Kinetics I & II

1. Describe what an enzyme is, the characteristics of enzymes, and thermodynamically how they increase the rate of a reaction. Define the terms: catalyst, activation energy, free energy of the reaction.

2. Describe how enzymes work using the terms: binding of the transition state, induced fit, covalent chemistry, metal ion chemistry, and general acid-base chemistry.

3. Define the terms cofactor and coenzyme.

4. Describe the significance of the terms Km and Kcat (know what it means if one enzyme has a lower or high Km than another, etc.) and estimate the value of Km from a graph of reaction velocity versus [S].

5. Describe four different types of inhibitors and, in general, how each works (competitive, uncompetitive, mixed, and irreversible).

6. Describe four types of enzyme regulation mechanisms and, in general, how each functions (allosteric, covalent modification, binding of another protein, proteolytic cleavage).

Epigenetics

1. Describe the four main characteristics of epigenetic phenomena.

2. Explain the basic principle of Waddington's epigenetic landscape.

3. List three specific examples of epigenetic phenomena.

4. Describe how DNA methylation can be inherited through cell division.

5. Name three chemical modifications to DNA or histones that can potentially be inherited.

6. Describe how epigenetic mechanisms and inheritance can occur both inside and outside the nucleus.

7. Name a specific type of gene that, when aberrantly methylated with 5meC, can lead to cancer and an approach to therapeutic intervention in this case.
Epithelia I
1. State the structural arrangements, classifications, and functions of epithelial tissues, and state their general structural relationships (orientation) to connective tissue, blood vessels, muscle, and neurons (peripheral nervous tissue).
2. Describe the epithelial to mesenchymal transition during development.
3. Describe the cellular basis for apical-basal polarity of epithelial cells and describe the functions of epithelial polarity.
4. State the different cell junctions that connect epithelial cells to one another and to the basal lamina, and describe their key components and functions.

Epithelia II
1. State the types and functions of the different cell surface modifications on epithelial cells.
2. Describe basal laminae by stating their basic components, their functions, the basis of their diversity, and their structural relationship to epithelia and other tissues.
3. Compare and contrast exocrine and endocrine glands in terms of their development, general structure, and functions. For both types of glands, trace the path that a secreted molecule must take from its synthesis to its destination, and describe all the barriers/structures the molecule must cross en route.

Epithelia III
1. Describe how epithelial tissues are maintained and regulated, and describe the properties, functions, regulation and development of epithelial stem cells.
2. State the general terms for epithelial-derived cancer, and describe how defects in epithelial cell regulation can contribute to cancer.
3. Describe how tissue sections are made and visualized for histological (microscope) examination, both for general staining and for specific staining of specific proteins and RNAs. Distinguish what general stains visualize from what immuno-staining or nucleic acid-staining techniques visualize. NOTE: Information on this objective is presented in the Intro-Epithelia Histo PDF (Histology lab material), and will also be presented in class.

Epithelial Transport
1. Explain the difference between the apical (a.k.a. mucosal / lumenal) vs. basolateral (a.k.a. serosal / peritubular) surface of the membrane.
2. Explain how pericellular transport works, and how it compares to transcellular transport.
3. Explain the mechanisms generating the driving force behind the transport.
4. Explain how nutrients are absorbed by the GI tract.
5. Explain how water absorption occurs.
**Extracellular Matrix & Cell Adhesion**

1. Discuss the contributions of the ECM to cell and tissue function.
2. Define the four major classes of ECM components and their properties.
3. Define two types of fibrillar proteins and at least two types of multidomain adapter proteins of the ECM.
4. Discuss the role of MMPs in ECM remodeling.
5. Discuss the role of adhesion in cell function and survival.
6. Define and describe at least three different types of cell adhesion molecules (CAMs) and their ligands.
7. Discuss the role of CAMs in signaling.
8. Describe proteins associated intracellularly with CAMs.
9. Discuss the ECM and cell adhesion in the context of disease processes.

**Finding Disease Genes**

1. Describe the types of genetic variation in the human genome and their frequency in the human population.
2. Recall the approximate number and frequency of different types of genetic variants in any random human.
3. Describe the technologies used to determine genetic variants in a person.
4. Describe the characteristics of Mendelian and Complex genetic diseases.
5. Describe strategies for mapping Mendelian and Complex disease genes.
6. Recognize limitations in strategies for mapping disease genes.
7. Discuss the concept of endotypic subgroups of complex diseases.

**Gates and Channels**

1. Describe the basic structure of Nav and Kv ion channels (number of subunits or repeats, number of membrane-crossing alpha helices per repeat/subunit) and whether this pattern is common to all known ion channels.
2. Describe the basic principles of channel selectivity, the features of ions that are important for selectivity, and the role of dehydration of the ions.
3. Describe specific structures of Nav and Kv channels that serve as the voltage sensors, the selectivity filter, and the activation/inactivation gates and describe where these gates are located with respect to the membrane orientation of Nav and Kv.
4. Describe what structural features of Nav and Kv lead to "sidedness" of agents that act on these channels and to "state-dependence" of action.
**Genetic Counseling**

1. Recognize the factors that have impacted the process of genetic counseling and how it is currently practiced.
2. Identify present day goals of genetic counseling.
3. Recognize indications for genetic counseling.
4. Identify fundamental ethical principles of genetic counseling as it is practiced today.
5. Recognize the reproductive options currently available for couples with increased risk for having a child with a genetic disorder, including which options are appropriate or available given the mode of inheritance and/or diagnostic information available.
6. Recognize factors that may impact a client’s perception of risk and their selected course of action.

**Genetic Testing**

1. Define what constitutes a "genetic test."
2. Describe the basic approaches, advantages, limitations, and interpretations of different types of genetic tests.
3. Interpret genetic testing results and distinguish between "informative" and "non-informative" results.
4. Explain how allelic heterogeneity and genetic heterogeneity can affect the performance of genetic tests.
5. Discuss the ethical and legal issues related to the confidentiality of genetic test results.

**Genome Editing**

1. Describe and distinguish between the following three genome-editing systems: Zinc Finger Nucleases (ZFNs), Transcription Activator-Like Effector Nucleases (TALENs), and Clustered Regularly-Interspaced Short Palindromic Repeats (CRISPR)/Cas9.
2. Identify the key components of the bacterial CRISPR/Cas9 system and describe how this system provides bacteria immunity from viral infection.
3. Discuss the similarities and differences between the two main methods of DNA repair that occur after genome editing: Nonhomologous End Joining (NHEJ) and Homology Directed Repair (HDR).
4. Select and justify which genome editing strategy is most applicable (based on strengths and weaknesses) to various disease models as we shall practice in the classroom session.
Genome Organization

1. Describe the fundamental principles regarding the evolution and organization of the human genome mentioned in the outline.
2. Explain why genome variation is an essential fuel of evolution and adaptation, but it also produces human disease.
3. Discuss the dynamic nature and non-random organization of the human genome as described in the outline.
4. Describe how frequently a SNP is likely to occur between two individuals.
5. Describe the types of variations that occur between genomes.
6. Describe the following characteristics of the genome: a) gene-rich; b) gene-poor; c) stable; d) unstable; e) GC-rich; f) AT-rich; g) euchromatic; and h) heterochromatic.
7. Describe how in genome sequencing focused on euchromatic regions, there is no completely sequenced & assembled human genome.
8. Discuss that many gaps still remain even in euchromatic regions.
9. Describe what categories genomic DNA sequences can be assigned to and the frequency of each class.
10. Describe the types, locations and frequency of repetitive DNAs that exist in the human genome.
11. Describe the estimated number and different types of human genes.
12. Discuss that genes often exist in families and gene families arise by gene duplication.
13. Discuss the advantages of gene duplication as an evolutionary mechanism.
14. Explain how evolutionarily advantageous increases in gene copy number can produce many diseases as a side effect.
15. Describe what the limitations are of current genome sequencing and screening methods, and how this relates to the "missing heritability" problem.

Histology Lab I & II

1. Describe how tissue sections are made and visualized for histological (microscope) examination, both for general staining and for staining with molecule-specific probes (antibodies and RNA probes). Distinguish what general stains visualize from what molecule-specific staining techniques visualize.
2. Identify and recognize cell nuclei in any tissue section, and identify material as within or outside of cells.
3. Recognize the internal spaces of big and small tubes and other tissue compartments, as well as the external edges of tissues when they are included in the section.
4. Compare and contrast the different cellular and extracellular elements within a given section to help recognize what is being seen.
5. Identify cells and structures of the basic tissues, and state their functions.
Introduction to Mendelian Inheritance

1. Explain and distinguish between Mendel's Laws of Inheritance
2. Discuss how the following two principal factors determine the inheritance patterns seen in single-gene disorders:
   a) quality of the phenotype (dominant vs. recessive), and
   b) location of the gene locus (autosomal vs. sex chromosome).
3. Recognize and distinguish between the major modes of Mendelian Inheritance, including autosomal dominant, autosomal recessive, X-linked dominant, and X-linked recessive.
4. Explain and compare various ‘threats’ to Mendelian inheritance patterns, particularly the threats due to variability in penetrance, expressivity, and pleiotropy.

Li-Fraumeni Vignette

1. Describe the criteria for classifying a hereditary cancer syndrome as Li-Fraumeni syndrome.
2. Describe the Knudson two hit hypothesis.
3. Describe the function of p53 in response to DNA damage.

Lung Cancer Vignette

1. Demonstrate the application of molecular biology into the clinic using lung cancer as an example.
2. How to implement molecular targeted therapies in the treatment of (lung) cancer.
3. How to select patients in order to give the right treatment to the right patient ("Personalized medicine" or "Precision medicine").
4. Differentiate between prognostic and predictive biomarkers.
5. Describe the status of lung cancer screening.

M2M Small Groups - Bench to Bedside I: Gaucher

1. Explain causes and risk factors of thrombocytopenia and it’s relevance to lysosomal storage and other disorders.
2. Explain causes and risk factors of hepatosplenomegaly and it's relevance to lysosomal storage and other disorders.
3. Explain the etiology of metabolic storage disorders and Gaucher disease (GD), including genetics.
4. Describe major subtypes of Gaucher disease (GD), including physical and neurological signs, ocular motor and other manifestations.
5. Describe cellular pathology and clinical manifestation of Gaucher disease (GD).
6. Explain how to diagnose Gaucher disease (GD).
7. Understand how to manage Gaucher disease (GD), and therapies that are currently available.
8. Describe limitations of current therapies for Gaucher disease (GD), including cost; discuss ethical issues of ERT and identify the current needs for GD.
M2M Small Groups - Bench to Bedside II: Scientific Method

1. Describe the scientific method.
2. Discuss and provide examples of the key elements of the scientific method.
3. Evaluate how the scientific method applies to medical research and clinical medicine.
4. Apply the scientific method to clinical reasoning.

M2M Small Groups - Research Ethics

1. Identify the three core ethical principles relevant to clinical research.
2. Apply the core ethical principles to a case.
3. Describe the basic functions of an IRB.

Membrane Fusion

1. Recognize the importance of sub-cellular protein targeting.
2. Describe the basic principles of membrane and viral fusion, including: a) the function and structure of SNARE proteins b) regulation of SNARE-based fusion c) the mechanism of viral fusion d) the regulation of viral fusion.

Membrane Potential

1. Compare qualitatively the relative strengths of electric and osmotic forces.
2. Describe the two forces acting on an ion moving across a membrane.
3. Define equilibrium potential.
4. Describe the difference between an equilibrium potential and a recorded membrane potential.
5. Recognize that each and every ion species has its own, independent equilibrium potential.
6. Answer correctly that the number of excess anions in a typical cell is small compared to the total number of anions.
7. Answer correctly that bulk solutions are always electrically neutral.
8. Describe how an artificial cell can be in a state of equilibrium even though the concentrations of ions are not the same inside and out.
9. Apply osmotic balance, charge neutrality, and the Nernst equation to calculate ion concentrations and the membrane potential of an artificial cell.
10. Differentiate between equilibrium and steady state.
11. Describe how membrane potential depends on relative, not absolute, permeabilities to ions.
12. Describe how the primary short term determinant of membrane potential is not the Na/K pump, but relative membrane permeabilities to the different ions.
14. Describe why, in neurons and other excitable cells, membrane potential is sensitive to small changes in [K+]o, but not [Na+]o.
15. Describe two treatments for hyperkalemia by which cells can be encouraged to take up potassium from the ECF.
Membrane Structure
1. Describe the molecular components of a membrane.
2. Describe the concept of membrane fluidity.
3. Identify the parts of a phospholipid, sphingolipid, and cholesterol.
4. Describe the asymmetry of membrane bilayers and provide at least two reasons that this asymmetry is functionally important.
5. List the different ways proteins associate with membranes.
6. Provide an explanation for the genetic basis of familial hypercholesterolemia, its relation to atherosclerosis, and the treatment for this disease.
7. Explain how cholesterol synthesis is regulated by gene transcription, cholesterol sensing in the ER and transcription factor release in the Golgi. How is the control of this pathway regulated by statins?

Membrane Transporters
1. Describe the difference between primary and secondary active transport.
2. Define cotransport and exchange transport.
3. Identify physical forces that can determine the gating properties of ion channel.
4. Determine if a pump for a particular ion must exist in a cell at rest (steady state), given an ion’s concentration inside and out, the membrane potential, and knowledge that the membrane is permeable to the ion in question; and, if a pump must exist, determine which direction it pumps the ion.
5. Describe how cells concentrate glucose inside, even though the glucose transporter cannot pump glucose against its concentration gradient.

Mitochondria
1. Describe the origin, basic structure and fission/fusion of mitochondria.
2. Describe the basic machinery of mitochondria import.
3. State the basic principles of electron transport and ATP production in mitochondria.
4. Explain the basic mechanisms of cell death regulation by mitochondria.
5. State the principles of mitochondria quality control.
6. Describe the role of mitochondria in senescence and some of the mitochondria-related diseases.

Mitosis and Cell Cycle I
1. Describe how cells regulate their size by coordinating growth with division at the Restriction point ("R") in G1 phase.
2. Recognize that the main goal of the somatic cell cycle is to ensure exact duplication of the genome in S phase followed by exact division of the genome in M phase to produce identical daughter cells.
3. Describe how cells prevent re-replication of their genomes by keeping the assembly and activation of replication complexes in separate cell cycle phases.
4. Recognize that genomic instability either by chromosome re-replication in S phase or mis-segregation during mitosis produces human diseases such as cancer and birth defects (trisomy 21).
Mitosis and Cell Cycle II

1. Compare the cell cycle of somatic cells (mitosis) with that of germ line cells (meiosis), which produces haploid gametes.
2. Recognize that differentiated, post-mitotic cells such as neurons are stuck at the "R" point in that they continue to grow without cycling.
3. Describe how alterations in many cell cycle regulators that are found in cancer cells are being used for patient diagnosis and prognosis.
4. Recognize the importance and the mechanism of cell cycle checkpoints in maintaining genomic stability.

Molecular Basis of Carcinogenesis I

1. Describe at least five different properties of malignant cancer cells.
2. Describe the multi-step process for carcinogenesis, and discuss the relative importance of heredity and the environment and why early events may include mutations in DNA repair genes.
3. Discuss the types of genes usually mutated in tumor initiation and their effect on cellular proliferation.
4. Describe at least two different examples for the type of cytogenetic abnormalities associated with malignancy.
5. Give at least two examples of events that can produce loss of heterozygosity and how they support Knudson’s theory.
6. Describe how cancers are associated with both dominant and recessive syndromes.
7. Describe how the RB (retinoblastoma) gene was first identified, including the important cytogenetic and molecular evidence.
8. List at least three biochemical properties of the protein product of the RB gene.
9. Describe how the RB protein functions during the cell cycle and why it is important in cancer; specifically how the loss of RB may produce a malignancy.
10. Describe the hallmark of a tumor suppressor gene or anti-oncogene and how this relates to the RB gene.

Molecular Basis of Carcinogenesis II

1. Explain why APC, BRCA1 and BRCA2 genes are tumor suppressors.
2. Describe why p53 was originally incorrectly thought to be an oncogene.
3. Explain why p53 is the "guardian of the genome."
4. Describe the cellular function of the p53 protein.
5. Recognize that oncogenic viruses make proteins to inactivate both Rb and p53.
6. Recognize HPV (human papilloma virus) as an example of an oncogenic virus in humans.
Molecular Basis of Carcinogenesis III

1. Discuss how oncogenes were discovered, describing at least three different examples of the method used in the discovery.

2. Discuss the functions of protein products of viral oncogenes, including at least four examples of oncogenes of known function.

3. Describe why oncogenes are useful as molecular markers in prognosis and discuss at least two examples of oncogenes that are currently being used, including the evidence of why these are good markers.

4. Differentiate between oncogenes and tumor suppressor genes and describe the function of these two types of cancer genes and how mutations in them may combine to produce cancers.

5. Describe two examples of how molecular, genomic, and clinical information (Bioinformatics) about a patient's cancer are being used for targeted therapy and for "personalized medicine" in cancer.

Molecular Cytogenetics

1. Recognize two of the most common leukemia translocations - one in chronic myeloid leukemia (CML) and one in acute pro-myeloid leukemia (APMO), and discuss the importance of these chromosomal findings that lead to biologically-based, targeted therapy (it's all in the genes!).

2. Describe the common cytogenetic findings in childhood B-cell leukemia and how the cytogenetic findings influence patient prognosis.

3. Delineate types of fluorescence in situ hybridization (FISH) probes and how they complement standard cytogenetic analysis, particularly in hematologic.

4. Explain the roles of chromosomal microarray (CMA) analysis in aiding certain genetic diagnoses and why CMA testing can detect genomic deletions or duplications, but not translocations.

5. Recognize laboratory test algorithm for children who present with learning disorders, developmental delays, autism, dysmorphic features, and/or failure to thrive.

Molecular Genetics of Hemoglobinopathies

1. Describe the layout of the α- and β-globin gene clusters and the switch between different forms of hemoglobin (Hb) during development. Explain the function of the locus control region (LCR).

2. Describe the mutations that cause sickle cell anemia and hemoglobin C disease and their consequences.

3. Describe the DNA diagnosis method of the sickle cell disease mutant allele.

4. Describe the six possible genotypes of α-globin locus, their clinical phenotypes, and the geographical distributions of α-thal-1 (−) and α-thal-2 (α−) alleles.

5. Describe the following concepts about β-thalassemias:
   (a) thalassemia major
   (b) thalassemia minor
   (c) β0-thalassemia
   (d) β+–thalassemia
   (e) β0-thal allele
   (f) β+–thal allele
   (g) simple β-thalassemias
   (h) complex thalassemias

6. Explain hereditary persistence of fetal hemoglobin (HPFH) and its clinical implications.

7. Give examples of two types of mutations that are known to cause HPFH.
MTOR
1. Describe the role of the PI3-kinase/Akt/mTOR pathway in normal cell function.
2. Describe the role of the PI3-kinase/Akt/mTOR pathway in cancer.
3. Discuss the role of mTOR inhibitors in clinical practice.
4. Discuss the impact of TSC1/2 mutations.

Multifactorial Inheritance
1. Identify and describe the characteristics of diseases and other traits that demonstrate multifactorial inheritance.
2. Give specific examples of diseases and other traits that demonstrate multifactorial inheritance.
3. Describe the strategies used to determine the relative importance of genetic vs. non-genetic factors in contributing to the variation in a complex trait.
4. Recognize the potential difficulties associated with quantifying the role of genetic factors in contributing to risk of disease at both the population level and the individual level.

Muscle I
1. Explain the structural basis of skeletal muscle contraction by constructing a sarcomere.
2. Describe the two regulatory proteins; specifically, where they are located and how they respond to changes in calcium concentration.
3. Describe the length of a sarcomere in resting muscle, contractile muscle, and muscle that is stretched almost to the point of injury (tearing) and discuss how this addresses the ambiguity of the question - "what is the length of a sarcomere?"
4. Describe the molecular basis of skeletal muscle diversity (fast and slow fibers) and the value of having this additional complexity.
5. Describe the key structural and physiological features of cardiac muscle and how they are similar to and different from skeletal muscle (sarcomere, regulatory proteins, events involved in a single contraction and relaxation, response to injury).
6. Explain why smooth muscle appears smooth and describe the key structural and physiological features of smooth muscle and how they compare to skeletal and cardiac muscle (contractile proteins, regulation of contraction, cell organization).
7. Describe how skeletal muscle develops (single cells going to multinucleate cells).
8. Explain the importance of the signaling protein myostatin and the consequences of mutations of myostatin.
9. Explain the molecular basis of familial hypertrophic cardiac myopathy, including the mutated proteins associated with this myopathy.
Muscle II

1. Explain how excitation-contraction coupling is accomplished for skeletal, cardiac and smooth muscle and why the t-system is not required in smooth muscle.

2. Define a myofibril and describe the relationship between myofibrils and the sarcoplasmic reticulum.

3. Starting with an action potential in a motor neuron, explain the processes required to have a skeletal muscle undergo a single contraction and relaxation (a twitch).

4. Explain the reason for the transverse-tubule system (t-system) in skeletal and cardiac muscle and how excitation-contraction coupling is accomplished in skeletal muscle.

5. Identify where motor nerve terminals associate with skeletal muscle fibers and describe the distribution of cells innervated by one motor neuron in a muscle.

6. Explain the molecular basis of malignant hyperthermia, the related protein mutation, the reason for the temperature rise, and the type of compound that will prevent the temperature rise.

7. Discuss the physiological and biochemical basis of skeletal muscle contraction, how contractile proteins work, and how they are regulated in skeletal muscle.

Muscle III

1. Identify muscle types that contain gap junctions and explain the role of gap junctions in these muscles.

2. Describe how tension is graded in cardiac and smooth muscle (two mechanisms) and how this is different from the gradation of tension for skeletal muscle.

3. Describe a muscle motor unit and how its average size relates to the function of that muscle.

4. Describe the two major mechanisms for how skeletal muscle tension is graded and regulated.

5. Define the role of "satellite cells" in skeletal muscle development and repair.

6. Describe the physiological and structural responses to exercise (or lack of exercise) on skeletal muscle (number of cells versus size of cells).

7. Explain the genetic and molecular basis of Duchenne muscular dystrophy, including the mutated protein associated with this myopathy and how this protein contributes to muscle structural integrity.

Muscular Dystrophy w/Patient Vignette

1. For the following three conditions, Hypertrophic cardiomyopathy, Malignant hyperthermia, and Duchenne Muscular Dystrophy:
   a) Recognize and distinguish the above phenotypes in patients.
   b) Explain how the molecular defect causes the abnormal muscle cell phenotype.

2. Identify and explain the triggers and treatment of malignant hyperthermia.

3. Describe the potential role of the manipulation of myostatin function in the treatment of muscular dystrophies.
**Mutational Mechanisms and Disease**

1. Describe, distinguish between, and give examples of the four major mechanisms that genetic mutations lead to disease:
   1) loss of function of the protein (most common)
   2) gain of function of the protein
   3) acquisition of a novel property by the mutant protein
   4) perturbed expression of a gene at the wrong time (heterochronic expression) or in the wrong place (ectopic expression), or both

2. Discuss and cite examples* of the eight steps at which mutations can disrupt the production of a normal protein.

3. Explain the mechanism of genetic anticipation in tri/tetra-nucleotide repeat disorder and recognize the phenotypes of these disorders.

**NextGen Sequencing**

1. Describe the major types of next-generation DNA sequencing.

2. Compare and contrast the types of data that next-generation DNA sequencers produce, in terms of read number and error rates.

3. Explain the key criteria that must be considered during analysis of next-generation DNA sequencing data for SNP identification.

4. Describe exome sequencing experiments and explain types of mutations that can be detected with this strategy.

5. Describe which types of diseases are best characterized by exome sequencing and which types of diseases are likely not diagnosable by exome sequencing.

**Non-Coding Regulatory RNAs**

1. Define and distinguish among miRNAs, siRNAs, and long non-coding RNAs.

2. Describe the biogenesis, mechanism of action, and functions of these RNAs.

3. Describe the role of Argonautes associated with small RNAs and their function.

4. Describe long non-coding RNAs and some known activities and cellular functions.

5. Describe the efforts and issues associated with using regulatory RNAs for treatment.

6. Describe antisense oligonucleotide therapeutics and their mechanisms of action.

7. Describe an example of a disease that might be treatable with small RNAs, how it would be treated, and the limitations.

**Nucleus and Nuclear Import and Export**

1. Describe the structure of the nuclear pore complex and roles of nucleoporins (Nups), karyopherins, and Ran in transport.

2. Describe the basic mechanisms of nuclear import and export of proteins and RNA/protein complexes, and how they can be regulated.

3. Explain how changes that impact nuclear transport and/or NPC components can contribute to disease.
Pedigree Analysis

1. Recognize and use common family history (pedigree) symbols.
2. Collect and draw a 3-generation family history using standard pedigree symbols.
3. Populate a family history with relevant medical phenotype information.
4. Discuss how the distribution of phenotypes in a pedigree is a reflection of the segregation of gene variants (genotypes).
5. Discuss potential ethical issues in the use and disclosure of pedigree information.

Peroxisomal Disorders

1. Understand the basic functions of the peroxisome.
2. Understand the concept of an inborn error of metabolism, and in particular how a single genetic defect may manifest as a multi-systemic disorder of peroxisomal metabolism.
3. Identify clinical features, causative genes, and potential therapies of several common Peroxisomal disorders including Zellweger spectrum disorders, Rhizomelic Chondrodysplasia Punctata Type 1, and X-linked Adrenoleukodystrophy.

Pharmacogenetics

1. Define and distinguish between pharmacogenetics and pharmacogenomics.
2. Explain the two major physiologic response to drugs, pharmacokinetics and pharmacodynamics, and briefly contrast Phase I and Phase II drug metabolism steps.
3. Explain the central role of the CYP450 enzyme system in drug metabolism.
4. Recognize and understand key specific pharmacogenetic examples from the text and this handout.
5. Recognize the truism of the axiom Variety is the spice of life!

Population Genetics

1. Define the field of population genetics and explain why "population-field" has relevance to doctors who often treat just "one patient" at a time.
2. Use basic principles of population genetics (estimate mutation rates, determine fitness, and understand effects of consanguinity and the addition of new mutations to gene pool).
3. Explain the assumptions required for Hardy-Weinberg principle to apply.
4. Apply the Hardy-Weinberg principle to estimate carrier frequencies for autosomal recessive disorders.
5. Discuss how physicians managing genetic diseases could affect the prevalence of genetic diseases.

Prader-Willi Vignette

1. Describe the chromosomal 15 abnormalities associated with Prader-Willi Syndrome (PWS) and how to test for them.
2. Describe the role of imprinting in disorders involving chromosome 15.
3. Describe the physical features (Phenotype) seen in a patient with Prader-Willi Syndrome.
4. Describe the medical problems seen in patients with Prader-Willi Syndrome.
5. Recognize and describe the developmental and behavioral phenotypes of a patient with Prader-Willi Syndrome.
6. Describe other common disorders associated with abnormalities on Chromosome 15q.
**Prion Vignette**

1. Explain the relationship between structures of the prion protein (PrP) and the infectious agents known as prions.
2. Describe how prion disease can be sporadic, inherited or infectiously acquired.
3. Explain what is meant by the concept of "prion strains".
4. Explain the possible relationship between prion disease and other human neurodegenerative diseases, at the level of protein structure.
5. Understand the biochemical basis of new diagnostic tests for prion diseases.

**RNA**

1. Distinguish purines and pyrimidine bases, ribose and deoxyribose, ribo- and deoxyribo nucleosides, nucleotides, nucleoside di and triphosphates.
2. Discuss the relative solubility of the components of nucleotides and the diseases related to their insolubility.
3. Identify the chemistry in the phosphodiester linkage of DNA and RNA polynucleotide strands. Unserstand the reason for 5'-3' polarity.
4. Discuss the important experiments that helped to establish DNA as the genetic material.
5. Describe the implications of Chargaff’s rules.
6. Describe the Watson-Crick three-dimensional model for DNA structure, recognize the major and minor grooves, the phosphodiester backbone and the base pairs.
7. Describe the chemical basis for the stability of the double helix DNA in solution.
8. Distinguish between linear and circular and relaxed and supercoiled forms of DNA.
9. Describe the chemical modifications of bases in DNA including different forms of DNA damage (methylation, deamination, depurination, UV cross linking) and their significance to disease.
10. Explain the chemistry of DNA polymerization and how nucleoside analogues are used as drugs.
11. Describe how DNA melting temperature/annealing to complementary sequence is negatively affected if there is a mismatch and how this can be taken advantage of in diagnostic techniques to distinguish the presence of a particular unique sequence using a "probe" that is completely complementary to that sequence.
12. Define the major similarities and differences between DNA and RNA.
14. Explain how puromycin mimics amino-acyl tRNA to terminate translation.

**RNA Synthesis**

1. Describe the chemical reaction catalyzed by RNA polymerase and why it is unidirectional.
2. Distinguish five steps in the transcription cycle common to bacterial and eukaryotic RNA polymerases.
3. Name the four cellular RNA polymerases and their main functions.
4. Define a promoter and name sequence elements characteristic of promoters in human genes.
5. Describe how α-amanitin and rifampicin block transcription.
6. Name four components of the RNA polymerase II pre-initiation complex.
7. Describe the clinical syndromes caused by mutations in TFIIH subunits.
RNA Synthesis and Splicing

1. Describe the three major ways in which most pre-mRNA's are processed.
2. Compare and contrast a pre-mRNA with a mature mRNA.
3. List the functions of the 5' cap of the mRNA.
4. List the three reactions required to add a 5' cap to pre-mRNA.
5. Recall the conserved sequences at the 5' and 3' ends of most introns and the consensus sequence at the polyA site.
6. Describe how alternative splicing permits multiple proteins to be produced by splicing defects.
7. Give examples of genetic disorders caused by splicing defects.
8. Describe the function of U1 and U2 snRNA's in splicing.
9. Identify on a diagram of a gene the following:
   a) transcription start site
   b) introns
   c) 5' splice sites
   d) 3' splice sites
   e) branch points
   f) exons
   g) 5' UTR
   h) 3' UTR
   i) initiation codon
   j) termination codon
   k) poly A site
10. Describe the two reactions that make the mature 3' end of mRNA's.
11. Describe the relationship between 3' end processing of the pre-mRNA and termination of transcription at the end of a gene.
12. Describe the two major functions of the mRNA's poly A tail.
13. Give an example of how alternative poly A sites can be used to make more than one protein from a single gene.

Secretory Pathways I & II

1. Describe the three mechanisms of protein transport.
2. List the major functions of the ER.
3. Describe co-translational translocation for the synthesis of cargo and transmembrane proteins.
4. List the major functions of the Golgi.
5. Name three well-studied vesicle coats and describe how these coats function in vesicular transport.
6. Explain the importance of protein retrograde movement from the Golgi back to the ER; describe one molecular mechanism for the retrograde movement.
Sex Development
2. Describe the clinical characteristics of disorders of sex chromosomes.
3. Describe the genetic regulation of sexual differentiation.
4. Describe the basic embryology of dimorphic human reproductive organs.
5. Describe the clinical approach to disorders of sexual differentiation.

Signaling Receptors
1. Draw the membrane topology a G protein-coupled receptor and identify the basic structural characteristics that mediate ligand binding and coupling to G proteins.
2. Explain how G protein-coupled receptors activate hetero-trimeric G proteins and diagram the GTP-hydrolysis cycle of G protein signaling.
3. Describe the function of second messengers in receptor signaling and give two examples for how they are generated by activated G proteins.
4. Explain how receptor activation leads to signal termination through receptor desensitization and coupling to additional pathways.
5. Give two examples of drugs that act through modulating different steps in a receptor-G protein-second messenger signaling cascade.

Signaling: Serine-Threonine Kinases and Phosphatases
1. Describe a phosphorylation reaction (including which amino acids can be phosphorylated) and explain how it can affect a phosphorylated protein.
2. List at least two other types of secondary protein modification
3. Explain the structure of an ATP molecule.
4. Explain how protein kinases can be classified and describe examples.
5. Describe the structure/function of a protein kinase and principles of their regulation (including requirement for activation loop phosphorylation in some but not all kinases).

Stem Cells & Differentiation
1. Explain the basics of stem cells, their niches, and the commitment (differentiation) of stem cells into different lineages.
2. Explain the concept of adult stem cell plasticity.
3. Explain the concept of reprogramming adult somatic cells into induced pluripotent stem (iPS) cells or embryonic-like stem cells.
4. Describe the role of stem cells in the initiation and maintenance of cancer.
Thalassemia Vignette

1. Recognize quantitative and qualitative changes in global chains.
2. Describe the geographic distribution of the common hemoglobin variants.
3. Identify the β thalassemia syndromes.
4. Identify the α thalassemia syndrome.

Toll-Like Receptors

1. Define: Pathogen Associated Molecular Pattern (PAMP) and Pathogen Recognition Receptor (PRR).
2. Match different Toll-like receptors (TLRs) with their cognate PAMPs.
3. Describe the basics of Toll-like receptor signaling pathways.
4. List examples of key genes and pathways activated by TLR signaling.
5. Explain the importance of subcellular localization of TLRs.
6. Explain, and provide examples of, how TLR signaling is relevant for human infectious and inflammatory disease.
7. Provide examples of how TLR agonists can be used therapeutically.
8. Provide examples of how TLR antagonists can be used therapeutically.

Tools of Molecular Biology I & II

1. Recall the classes of enzymes that are used in recombinant technology to: a) copy a DNA sequence into a DNA sequence, b) copy an RNA sequence into a DNA sequence, and c) join DNA fragments.
2. Describe the three main stages that are repeated during PCR amplification. State the approximate temperature of each step, and relate this temperature to the state of the DNA molecules in the PCR reaction.
3. Describe at least 1 distinct use for PCR amplification in the diagnosis of a genetic condition in your patients.
4. Compare and contrast the molecular details of the processes of DNA sequencing and PCR amplification on in a short paragraph.
5. Describe how DNA detection during quantitative (“real-time”) PCR is accomplished.
6. Be aware of the different types of cloning vectors and their general features.
7. Describe the use of microarrays for measuring levels of mRNA (e.g. gene expression).
8. Write out three palindromic double-stranded DNA sequences that are likely to be cut by restriction endonucleases (a known restriction enzyme does not have to exist for your sequences).
9. Explain the principle of electrophoretic separation of DNA to a pre-med student.
10. Give an example of a disease that can be diagnosed using a restriction fragment length polymorphism (RFLP) and a use of DNA fingerprinting. Describe at least three experimental stages required in each of these procedures.
11. List the names given to the transfer of DNA, RNA and protein respectively from an electrophoresis gel to a membrane.
12. Describe three characteristics of a hybridization probe that you will use to detect a specific DNA sequence on a membrane.
Translation I & II

1. Name and describe the roles of the parts of the machinery that drives translation, specifically: ribosomes, mRNA, tRNA, aminoacyl tRNA synthetases, initiation factors, elongation factors, and release factors.

2. Be able to explain the nature of the genetic code, how it is read, and the effects of mutations to the mRNA. Name the start codon and what amino acid it encodes.

3. Describe the four phases of translation: initiation, elongation, termination, and ribosome recycling, and describe the basic elongation cycle.

4. Identify the important differences between bacterial and eukaryotic translation, especially in regard to initiation.

5. Explain the significance and effects of the following processes: cap-independent initiation, interferon stimulation, mRNA editing, rapamycin treatment, eIF2-alpha phosphorylation. Be able to describe when these might be important.

6. Identify antibiotics that operate by affecting translation.

7. Describe how intracellular levels of iron can be regulated by translation, using this as an example of how protein-mRNA interactions regulate translation.

Treatment of Genetic Diseases

1. Discuss that while curing genetic diseases remains challenging, many genetic diseases are amenable to some level of treatment/management.

2. Identify genetic conditions that currently can be treated and those for which treatment may soon be available.

3. Discuss examples of genetic disorders that are treated on the basis of protein/enzyme replacement therapy.

4. Identify the principles and theoretical risks of gene therapy.

5. Identify the financial, ethical, social, economic and legal issues raised by specific therapies for genetic illnesses.

Turner Syndrome Vignette

1. Recognize the clinical presentation of patients with Turner Syndrome.

2. Enumerate challenges across the lifespan in patients with Turner Syndrome.

3. Identify pitfalls of the medical culture in dealing with patients with Turner Syndrome.

Tyrosine Receptor Kinases

1. Describe mechanism of receptor tyrosine kinase (RTK) activation.

2. Explain molecular mechanism of stimulation of ras GTPase by RTKs.


4. List tumor cell characteristics that predict clinical response to EGFR-targeted therapeutics.

5. Describe mechanism of resistance to TKI's such as EGFR inhibitors.
Vasculature

1. Describe the structure, organization, and function of the basic layers of blood vessel walls.
2. Discuss the morphological characteristics that distinguish the different types of blood vessels.
3. Explain the structure and function of the different types of capillaries.
4. Outline the unique functions of post-capillary venules.
5. Describe how blood flow is regulated in capillary beds.
6. Discuss the general structure and functional significance of arterio-venous shunts, portal systems, pampiniform plexus, anastomoses, and end arteries.

Von Hippel-Lindau Clinical Vignette

1. Recognize the clinical manifestations of Von Hippel-Lindau (VHL) disease.
2. Learn the molecular basis of Von Hippel-Lindau (VHL) disease and the pathogenesis of clear cell renal cell carcinoma.
3. Understand the molecular rationale for therapies used to treat clear cell renal cell carcinoma and how these targets were identified through understanding diseases such as VHL.

X-Linked Recessive Inheritance and Mitochondrial Diseases

1. Distinguish the differences between X-linked dominant and X-linked recessive inheritance.
2. Describe the characteristics of an X-linked pedigree.
3. Describe the unique features of mitochondrial inheritance and the clinical manifestations of these mutations.
4. Recognize and describe the clinical features and molecular basis of Hemophilia A, Duchenne Muscular Dystrophy and Fragile X Syndrome.
5. Describe X chromosomal inactivation and its complications.