

# Apheresis & Ethics

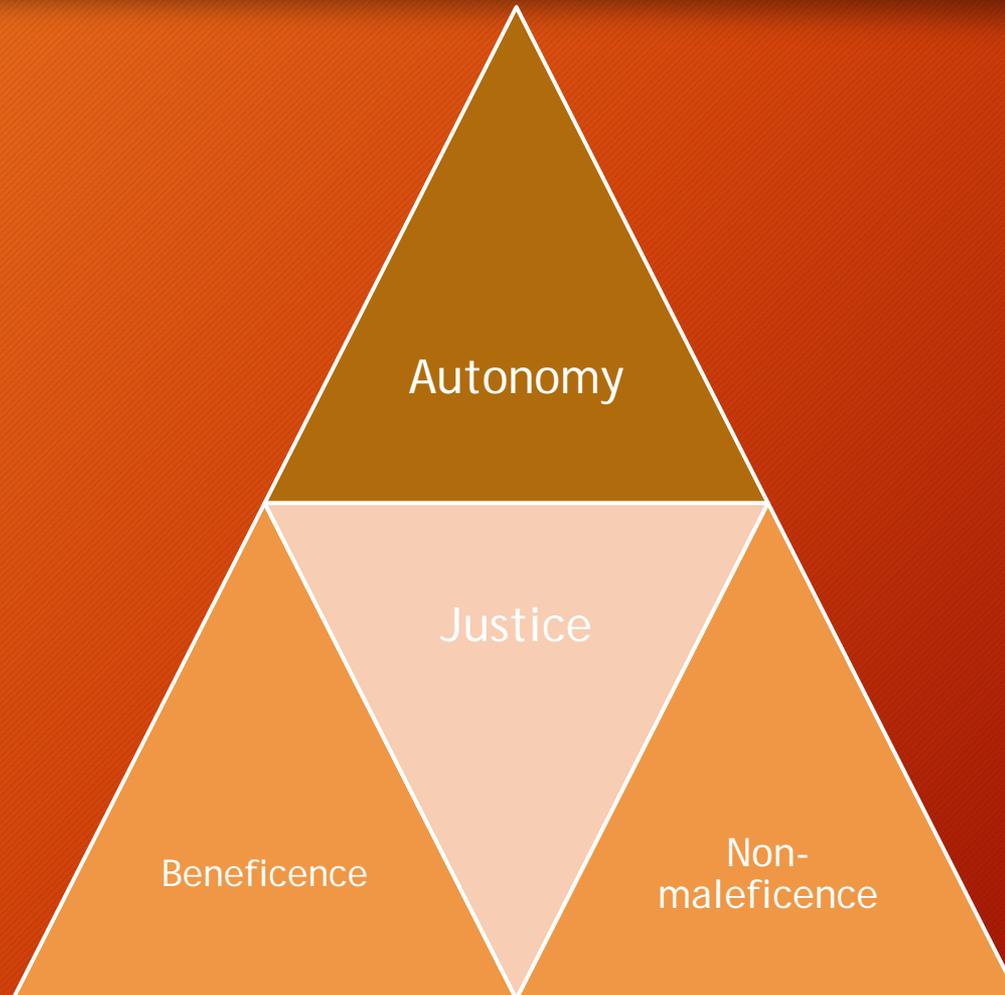
Andrew D. Jones, MD

April 2018

# Learning Objectives

- 1) Review how to obtain proper informed consent from patients requiring therapeutic apheresis.
- 2) Discuss the evaluation of risk-benefit ratio especially in patients with Category 3 or Category 4 indications.
- 3) Review the ethical issues surrounding collection of hematopoietic progenitor cells (HPCs) by apheresis from related donors

# Principles of Bioethics





# Non-maleficence

- *Primum non nocere*
- "Above all, do no harm"
- Sometimes attributed to Code of Hammurabi
- ...and Galen
  - Latin?
- ...and Hippocrates / Hippocratic Oath
  - Latin?
- ...and Ambrose Paré
  - Latin?



# Non-maleficence

- Likely Thomas Sydenham (1624-1689)
  - “Father of English Medicine” and “The English Hippocrates”
  - Wrote in English, translated to Latin, and back to English
- Quoted in Thomas Inman’s “Foundation for a New Theory and Practice in Medicine”
- Common by 1860

# Non-maleficence and Negligence

- Negligence:
  - Duty to the affected party
  - Breach of that duty
  - Affected party is harmed
  - Harm caused by breach of duty

“ V. A physician shall continue to study, apply, and advance scientific knowledge, maintain a commitment to medical education, make relevant information available to patients, colleagues, and the public, obtain consultation, and use the talents of other health professionals when indicated. ”

AMA Code of Medical Ethics, June 2001 revision



### Time on Apheresis Rotation

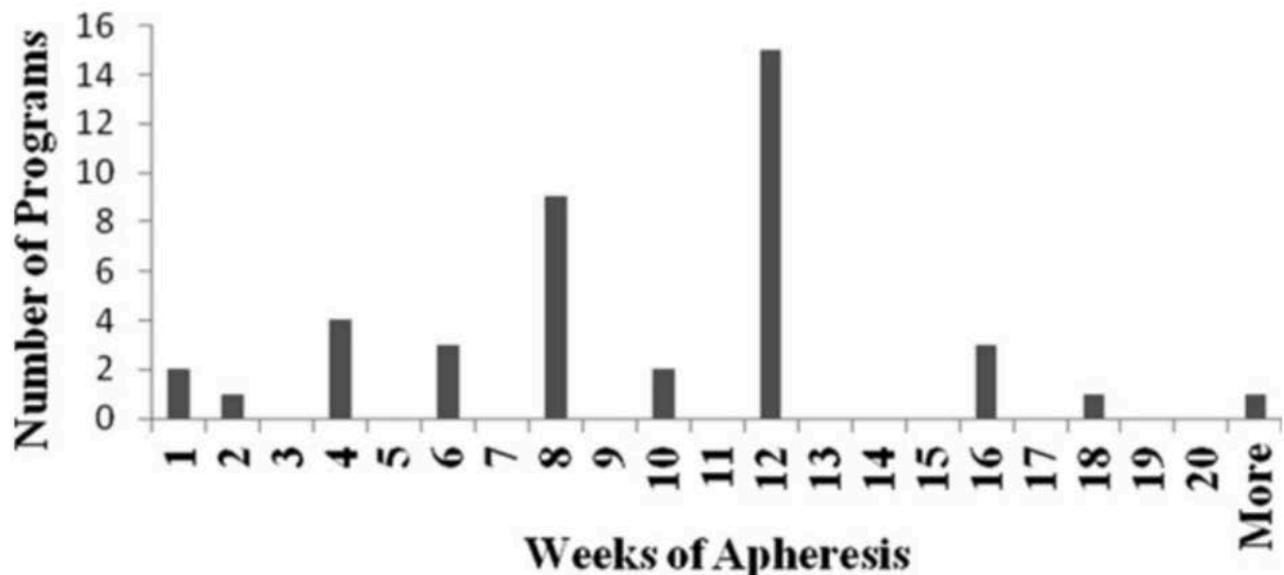


Fig. 1. Responses to Pathology Resident Director survey on Resident Apheresis Education.

Marshall, C et al. "Milestones in Apheresis Education." *J Clin Apher* 27:242-246 (2012).



ABOUT ASFA ▾

MEMBERSHIP ▾

FORUMS

EDUCATION ▾

RESOURCES ▾

MEETINGS ▾

CAREER CENT

## Qualification in Apheresis (QIA)

### ●●● Qualification in Apheresis (QIA)

ASFA is pleased to offer a Qualification in Apheresis (QIA) in partnership with The Board of Certification (BOC) of the American Society for Clinical Pathology (ASCP) as of January 2016!

<http://www.apheresis.org/?page=QIA>

# Beneficence

- William Frankena's 4 obligations:

One ought not to inflict evil or harm

One ought to prevent evil or harm

One ought to remove evil or harm

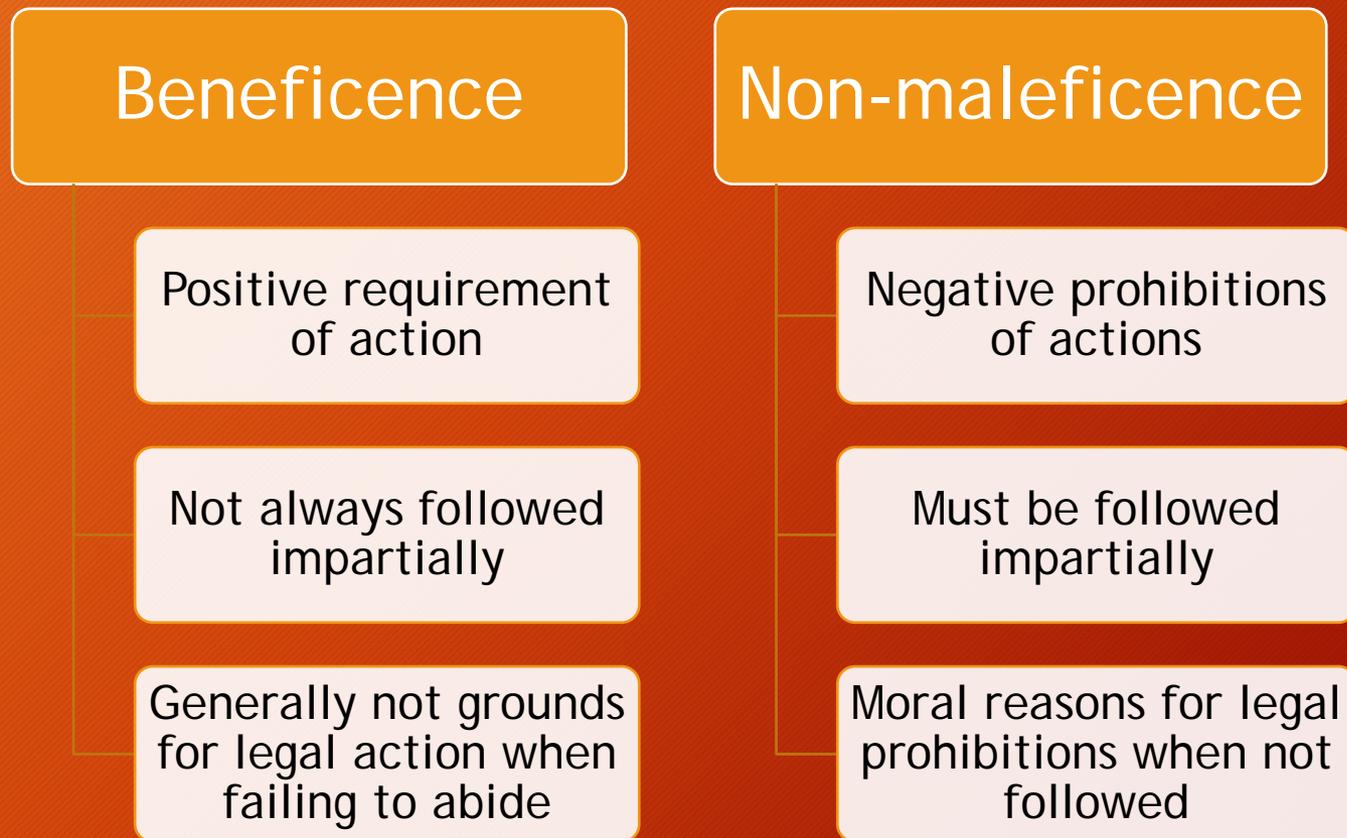
One ought to do or promote good



# Beneficence & Obligation

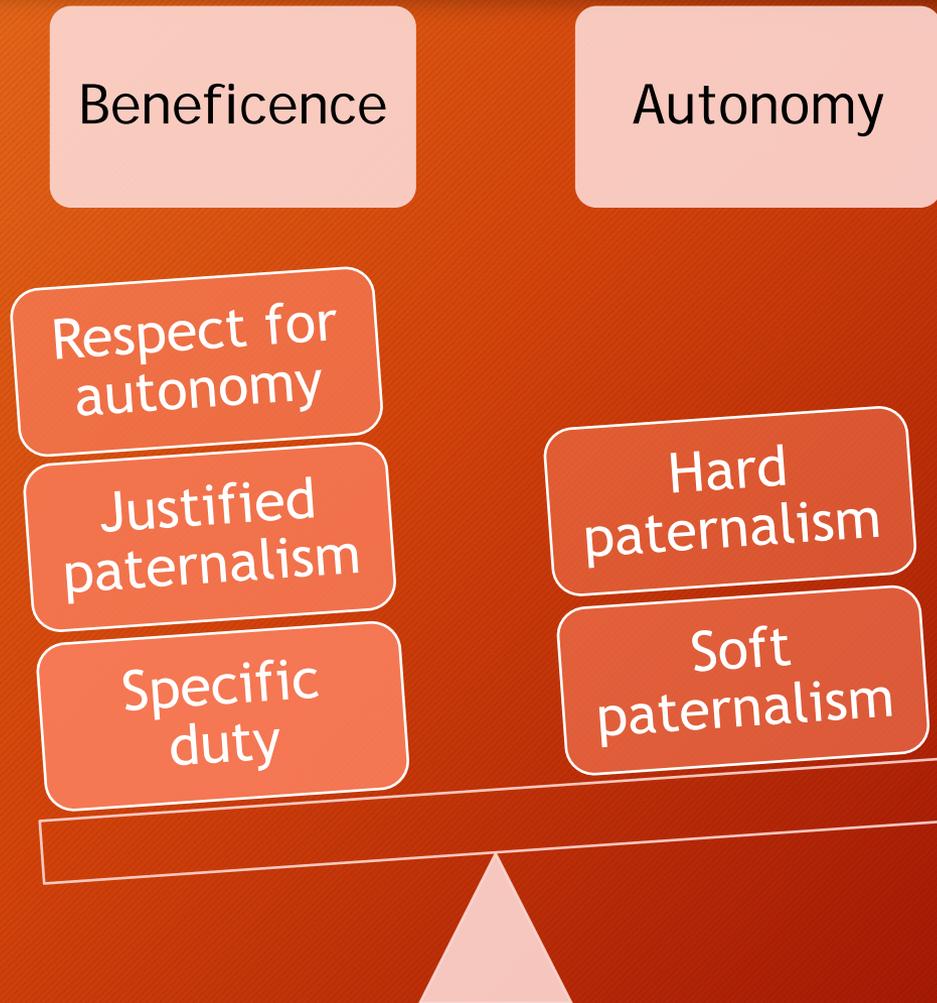
1. Y is at risk of significant loss
2. X's action is necessary to prevent the loss
3. X's action is likely to prevent the loss
4. X's action would not present significant risks, costs, or burdens to X
5. The expected benefit to Y outweighs likely cost to X

# Beneficence vs Non-maleficence





# Beneficence & Paternalism





# Autonomy

- Nuremberg
- Joseph Fletcher
- Shift authority from duty of physician to patient rights
- Medical ethics → Bioethics
  - Research
  - Genetics
  - Transplantation
  - Life support
  - Scarcity of resources, drugs, & technology
  - Definition of death



# Autonomy

1. Acting with intentionality, and
2. Acting with understanding, and
3. Acting without controlling influences that determine action.

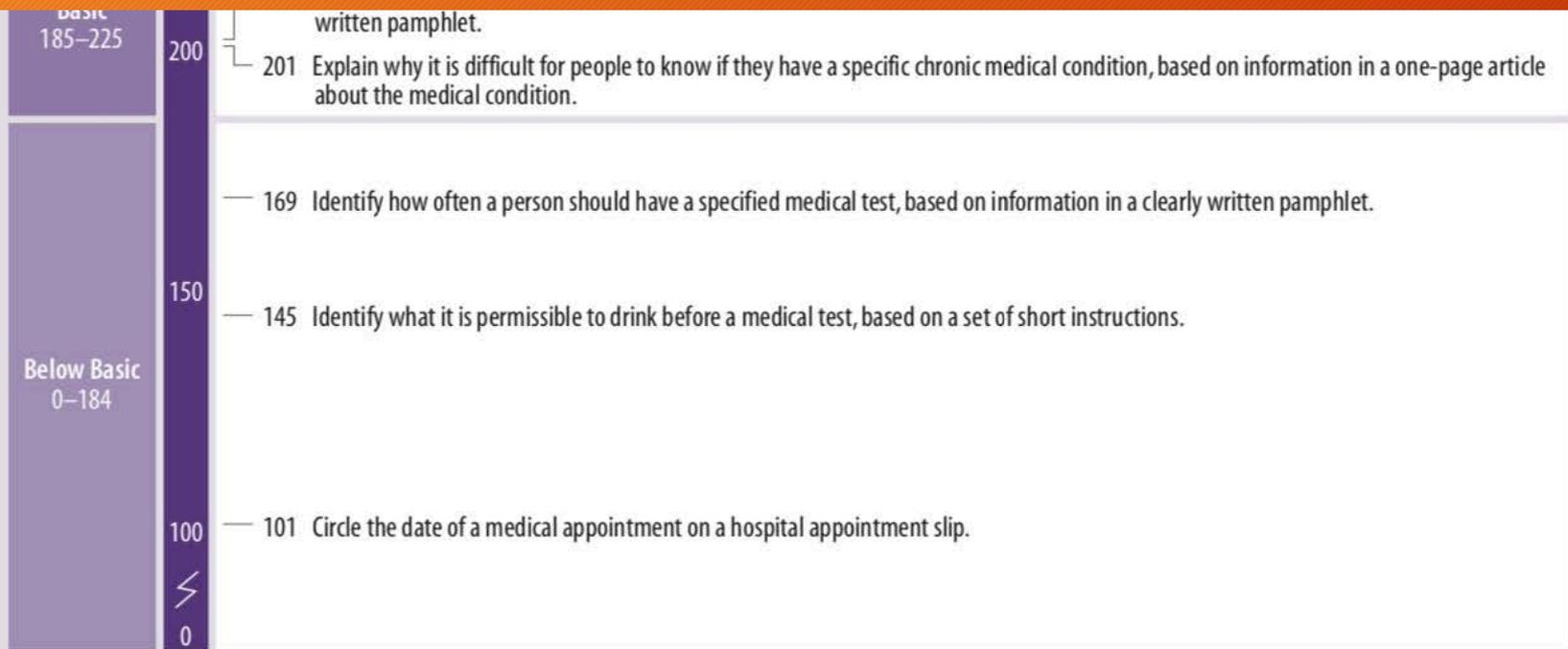


# Autonomy: Informed Consent

- Release → Consent
- Tort law
  - Battery and negligence
  - Professional standard vs material risk
  - Subjective standard
- Signature is necessary but not sufficient
- Must convey a realistic assessment of utility of procedure

# Elements of Informed Consent

- “Just right” amount of information
- Providing information at an appropriate level
- Providing information in an appropriate language
- Facilitating understanding with opportunities for questions
- Ongoing process
  - Before, during, after signature
- Providing information as situation changes
- Minimizing coercion / undue influence



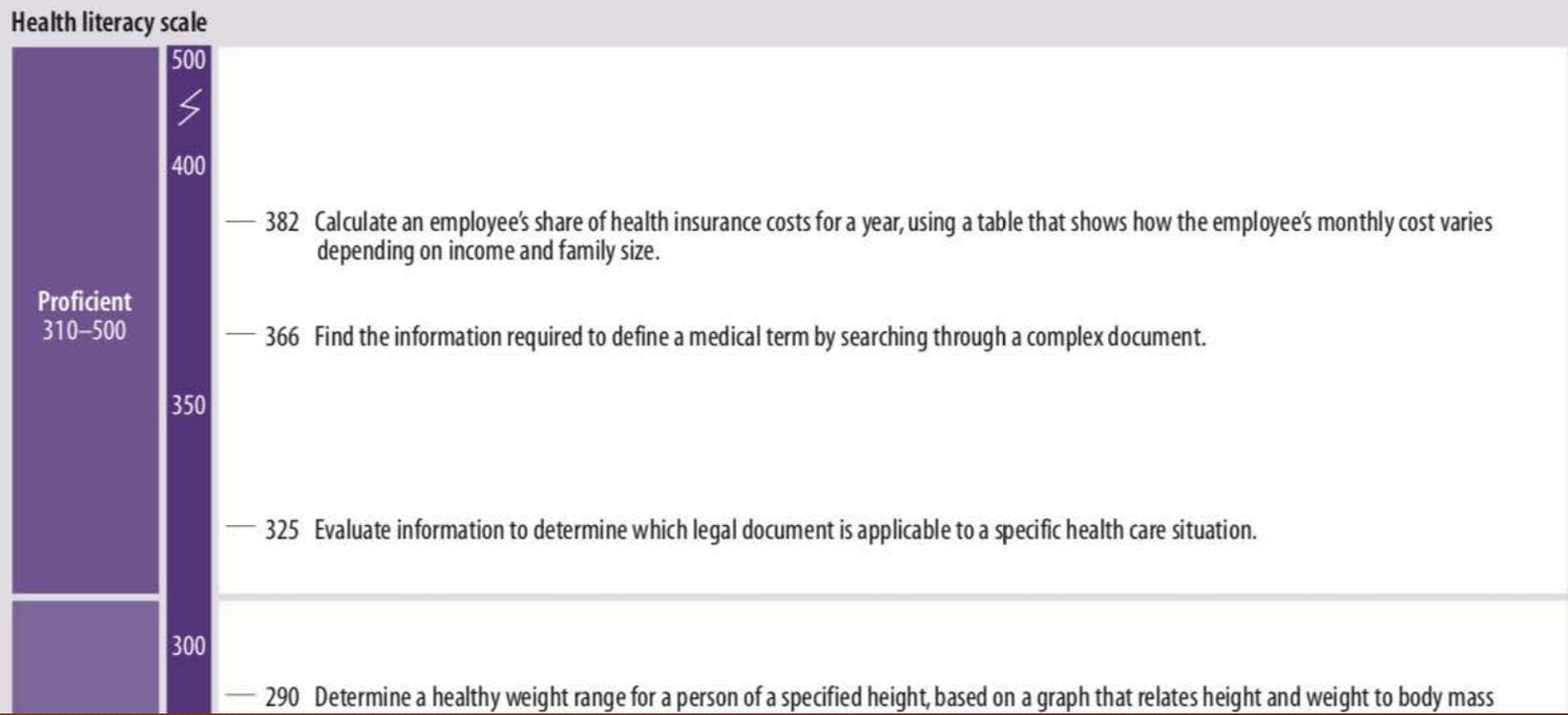
NOTE: The position of a question on the scale represents the average scale score attained by adults who had a 67 percent probability of successfully answering the question. Only selected questions are presented. Scale score ranges for performance levels are referenced on the figure.

SOURCE: U.S. Department of Education, Institute of Education Sciences, National Center for Education Statistics, 2003 National Assessment of Adult Literacy.

# Informed Consent & Health Literacy



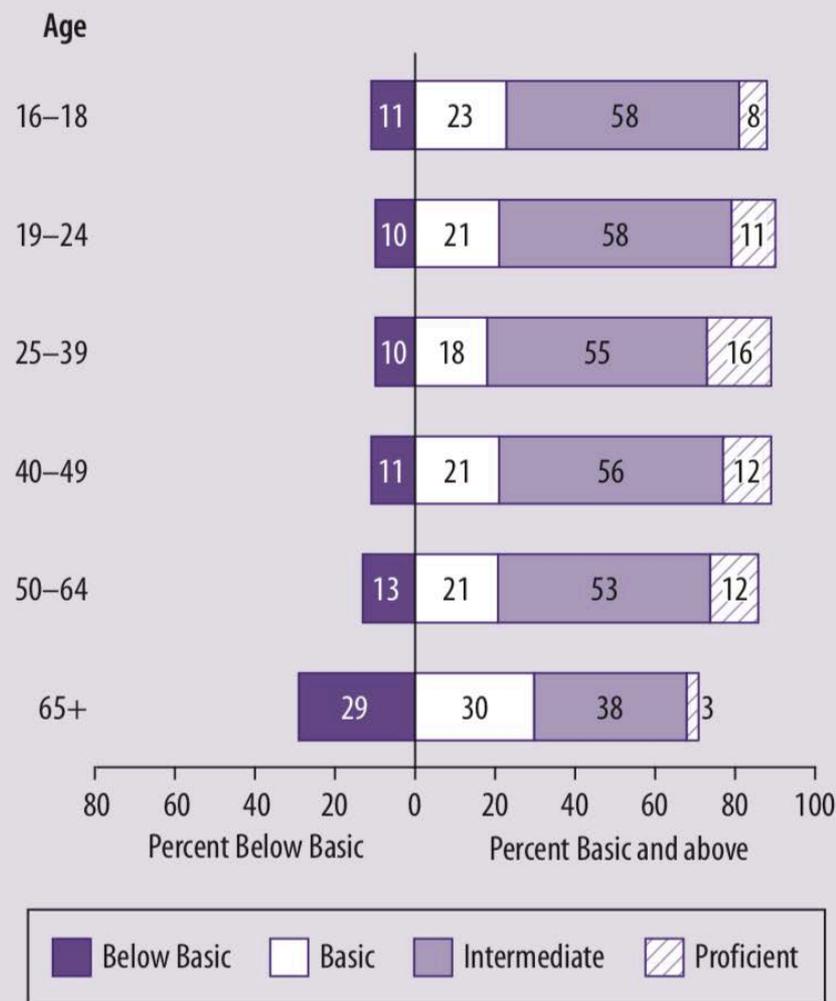
Figure 1-1. Difficulty of selected health literacy tasks: 2003



# Informed Consent & Health Literacy

# Informed Consent & Health Literacy

Figure 2-7. Percentage of adults in each health literacy level, by age: 2003



NOTE: Detail may not sum to totals because of rounding. Adults are defined as people 16 years of age and older living in households or prisons. Adults who could not be interviewed because of language spoken or cognitive or mental disabilities (3 percent in 2003) are excluded from this figure. SOURCE: U.S. Department of Education, Institute of Education Sciences, National Center for Education Statistics, 2003 National Assessment of Adult Literacy.



# Autonomy: Informed Consent

- Training for medical professionals
- Review of process by laypeople
- “Disinterested” person
- When results are expected
- Include discussion about blood products



# Autonomy

- Cultural differences
  - 47% of Korean-Americans believed a patient should be told a diagnosis of metastatic cancer vs 87% of white Americans
  - Tendency to believe family should make decisions about life support and terminal care
- Language shapes reality
  - Navajo patients may understand risks to be made real and dangerous by speaking

Hofmann, J. "Principles of Apheresis Technology." 6<sup>th</sup> ed.

Blackhall, et al. JAMA. 1995;274(10).

Beauchamp *et al.* "Principles of Biomedical Ethics." 7<sup>th</sup> ed.

# Justice

- Difficult to define, typically used in combination(s)
- Four traditional theories:
  - Utilitarian
  - Libertarian
  - Egalitarian
  - Communitarian
- Two contemporary theories:
  - Capabilities
  - Well-being

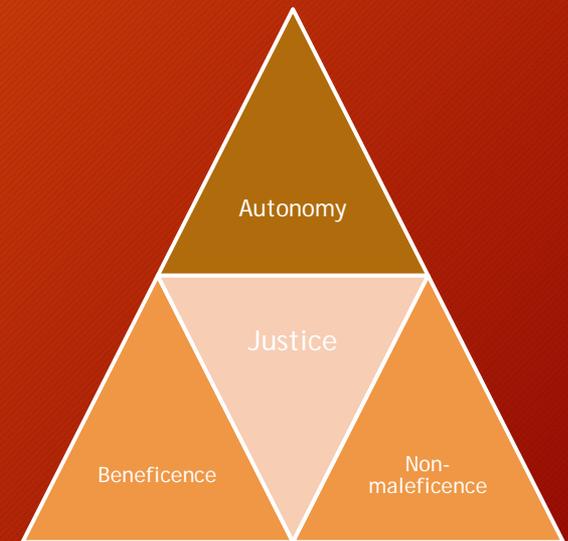


# Justice

- Typically, distributive
- Ensuring consistent access and care
- Written procedures
- Checklists
  - Procedure based
  - Ethics based

# Critiques of Principlism

- Ignores emotional and situational decision-making
- Oversimplifies
- Excessive claims of universality
  - Based on “common morality”
- Cultural pluralism left behind
- Difficult to operationalize





# Application: SFNO Method

- Four steps
- Apply ethical principles
- Help in evaluating principles and adjudicating options
  - Stakeholders
  - Facts
  - Norms
  - Options

# SFNO Steps

1. State the question or dilemma to resolve.
2. Organize the information (SFNO)
3. Identify where the primary conflict lies.
4. Adjudicate between competing stakeholders, facts, and/or norms.

# Case 1

Missing Indications

# Case 1

You are consulted by internal medicine and asked to perform Therapeutic Plasma Exchange (TPE) on a patient with thrombotic microangiopathy recently started on a new targeted therapy as part of a clinical trial. The patient is thrombocytopenic (45k) and anemic (Hb 7.1) but stable and not bleeding. The patient is apprehensive about the procedure, but will do what you recommend.

# Case 1: Step 1

- The dilemma: Should TPE be performed on a patient without a category or grade indication?

# Case 1: Step 2

- Stakeholders:
  - The patient, because his life is at stake.
  - The medicine team, because they are obligated to act in the best interest of the patient.
  - The apheresis team, because they are charged with assessing the clinical situation vis TPE, and in acting in the best interest of the patient.
  - Society / future patients, because knowledge gained may help treat future patients.

# Case 1: Step 2

- Factors

- T
- G
- T
- f
- T
- l
- I
- C
- T
- t

**TABLE II. Category Definitions for Therapeutic Apheresis**

Category	Description
I	Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
II	Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment.
III	Optimum role of apheresis therapy is not established. Decision making should be individualized.
IV	Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful. IRB approval is desirable if apheresis treatment is undertaken in these circumstances.

# Case 1: Step 2

- Norms:
  - Autonomy: The patient is able to decide, but wants to defer judgement to you.
  - Beneficence: Possible benefit could be robust recovery or no benefit at all. The patient will likely require platelets prior to TPE.
  - Non-maleficence: Bleeding and complications of anemia could occur during or after the procedure. Transfusions expose the patient to blood products.

# Case 1: Step 2

- Options:
  - Do not perform TPE and continue medical management (steroids, supportive care)
  - Perform TPE for a limited series (3 procedures, every other day for 5 days) and evaluate the patient carefully. Determine next steps based on clinical response.
  - Trend clinical course and re-evaluate in 24-48 hours.
  - Only perform TPE if the patient's status declines despite medical management.

# Case 1: Step 3

- Where is the conflict?
  - The conflict here is with facts and norms



# Case 1: Step 4

- To resolve this dilemma, we should try to gather more information:
  - What is the drug's MOA?
  - Is TPE likely to clear the drug?
  - How sure are we that the TMA is caused by the drug? Are there other possibilities? (e.g. TTP, PTP, overcall of schistocytes on smear, etc)
- We must balance beneficence and non-maleficence
  - Tolerance for risk directly proportional to likelihood of potential benefit.

# Case 2

Palliative Apheresis

## Case 2

Your patient is an adult male with a history of ALL. He has failed multiple rounds of medical therapy and the clinical team is discussing goals of care with the family. The patient is currently stable and has been mostly asymptomatic for several days, but will likely transition to palliative care. However, the clinical team would like leukoreduction to continue to reduce / prevent symptoms of leukostasis.

# Case 2: Step 1

- The dilemma: Should leukopheresis be continued with no reasonable expectation of recovery?

# Case 2: Step 2

- Stakeholders:
  - The patient, who is dying and has decided to not pursue chemotherapy but wishes to continue leukoreduction.
  - Health-care providers, because we are obligated to act in the best interests of the patient with limited resources.
  - The family, who wishes their loved one to have as comfortable and peaceful a death as possible.

# Case 2: Step 2

- Facts:

- Leukoreduction reduces WBC counts by 30-60% and is a Category II recommendation for symptomatic hyperleukocytosis (Category III for prophylactic / secondary).
- Definitive management of ALL is chemotherapy; the role of leukoreduction is indicated to improve tissue perfusion and reduce pulmonary and CNS leukostasis.
- Without chemotherapy, blasts rapidly accumulate necessitating daily procedures with significant interval WBC increases.

# Case 2: Step 2

- Norms:
  - Beneficence: Leukopheresis may ease or delay the patient's symptoms.
  - Autonomy: The patient desires palliative leukoreduction to prevent symptoms of leukostasis.
  - Family / Community: The procedure may give the family time to reconcile the goals of care with other palliative care options.
  - Justice: Apheresis machines, staff, and blood bank supplies are limited and typically utilized for therapeutic (not palliative) purposes.

# Case 2: Step 2

- Options:
  - Refuse to perform palliative leukoreduction.
  - Agree to perform one leukoreduction as a last therapeutic measure before starting palliative care.
  - Agree to perform a limited series of leukoreductions with a pre-defined end date.
  - Agree to perform leukoreductions as long as the patient has a WBC count greater than  $100 \times 10^9$  regardless of goals of care.
  - Explore alternatives in palliative care that could alleviate symptoms without invasive procedures.

## Case 2: Step 3

- Where is the conflict?
  - In this case, the conflict is primarily within norms.



# Case 2: Step 4

- Adjudicating between norms requires testing a tentative conclusion:
  - Perform one final leukoreduction
- 1. Necessity: It is necessary to infringe on the just distribution of scarce therapeutic resources to achieve this goal.
- 2. Effectiveness: The goal will be effective in bridging the patient to palliative care.
- 3. Proportionality: The desired goal is more important than our claims to distributive justice.
- 4. Least infringement: This conclusion will minimize the infringements on justice (as compared to doing a series of procedures).
- 5. Proper process: The decision has been made in consultation with the providers, patient, and family.

# Case 3

Family Mismatch

## Case 3

A close-knit family of 4 presents for HLA testing to see if a family member is a match for a child needing a marrow transplant. The parents have been together for over 20 years and had no children prior to their relationship. Subsequent HLA testing shows the potential donor sibling, a teenager, cannot be a genetic relative of the father.

# Case 3: Step 1

- The dilemma: Should the mother, father, and/or the teenage child be told the details of the HLA test result?

# Case 3: Step 2

- Stakeholders:
  - The teenager, who cannot be a match for donation.
  - The mother, who is genetically related to the teenager.
  - The father, who is not genetically related to the teenager.
  - The sibling, who cannot receive a transplant from the teenager.
  - The health care team, who are obligated to act in the best interest of patients and donors.

# Case 3: Step 2

- Facts:
  - HLA testing is more accurate at determining when someone is not a genetic relative than when someone is.
  - Disclosing the test result details will not result in a match for the sibling.

# Case 3: Step 2

- Norms:
  - Autonomy: adult patients have a right to know their test results, though this teenager is neither the patient nor an adult.
  - Non-maleficence: physicians have a duty to not withhold test results from patients.
  - Family: revealing the results could have a significant impact on this close-knit family.

# Case 3: Step 2

- Options:
  - Do not inform the family of the test result details.
  - Inform the mother of the test result details.
  - Inform both parents of the test result details.
  - Inform the teenager of the test result details.
  - Inform the teenager and the parents of the test result details.
  - Inform the entire family of the test result details.

## Case 3: Step 3

- The conflict here lies in stakeholders, between the family members, and in norms, between non-maleficence and autonomy.

# Case 3: Step 4

- Adjudicate between competing interests:
  - Stakeholders
    - Are there reasons to prioritize the interests of one stakeholder over another?
    - Who ultimately has decision-making authority?
  - Norms
    - Is infringing on a norm or value **necessary**?
    - Will the action be **effective** in achieving the desired goal?
    - Is the goal **proportionally** important enough to justify overriding another principle or value?
    - Will the action **minimize infringement** on conflicting principles or values?
    - Has the decision been made using the **proper process**?

# Case 4

Misinformed Consent

# Case 4

- A senior pathology resident was asked to see a patient on-call for emergent leukopheresis. He obtained a history, performed a physical exam, and obtained the patient's consent for emergent leukoreduction. After the successful completion of the procedure, he is noted to surreptitiously add additional possible adverse events to the consent form before placing it in the bin to be scanned into the patient's chart.



# Case 4: Step 1

- The issue: It's unclear whether the patient gave appropriate informed consent, and whether the resident falsified the consent document.



# Case 4: Step 2

- Stakeholders
- Facts
- Norms
- Options



# Case 4: Step 3

- Where is the primary conflict?



# Case 4: Step 4

- Adjudicate
  - Facts
  - Norms
    - Is infringing on a norm or value **necessary**?
    - Will the action be **effective** in achieving the desired goal?
    - Is the goal **proportionally** important enough to justify overriding another principle or value?
    - Will the action **minimize infringement** on conflicting principles or values?
    - Has the decision been made using the **proper process**?

# Case 5

Missing Diagnosis

# Case 5

- You are consulted by the neurology team regarding a challenging patient. They believe the patient has a neurologic and/or rheumatologic disease that could benefit from plasma exchange, but the diagnosis is elusive (all serologic studies are negative to date). They insist on starting plasma exchange urgently.

# Case 5: Step 1

- The issue: should TPE be started on a patient without a confirmed diagnosis or indication?



# Case 5: Step 2

- Stakeholders
- Facts
- Norms
- Options



# Case 5: Step 3

- Where is the primary conflict?



# Case 5: Step 4

- Adjudicate
  - Facts
  - Norms
    - Is infringing on a norm or value **necessary**?
    - Will the action be **effective** in achieving the desired goal?
    - Is the goal **proportionally** important enough to justify overriding another principle or value?
    - Will the action **minimize infringement** on conflicting principles or values?
    - Has the decision been made using the **proper process**?