Thoughts on Gene Editing

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U.S. National Academies Human Gene Editing Committee

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Topics for Discussion

- NIH Recombinant DNA Advisory Committee (RAC) process and recent discussion of CRISPR protocol
- *In utero* gene therapy/gene editing
- Other gene editing topics of interest to the Committee

NIH RAC Process and Recent Discussion of CRISPR Protocol

NIH Framework for Oversight of Somatic Cell Gene Editing Research

- Biosafety guidelines
  - *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*
- Advisory body
  - NIH Recombinant DNA Advisory Committee (RAC)
- Local review of risks and implementation of *NIH Guidelines*
  - Institutional Biosafety Committees

RAC

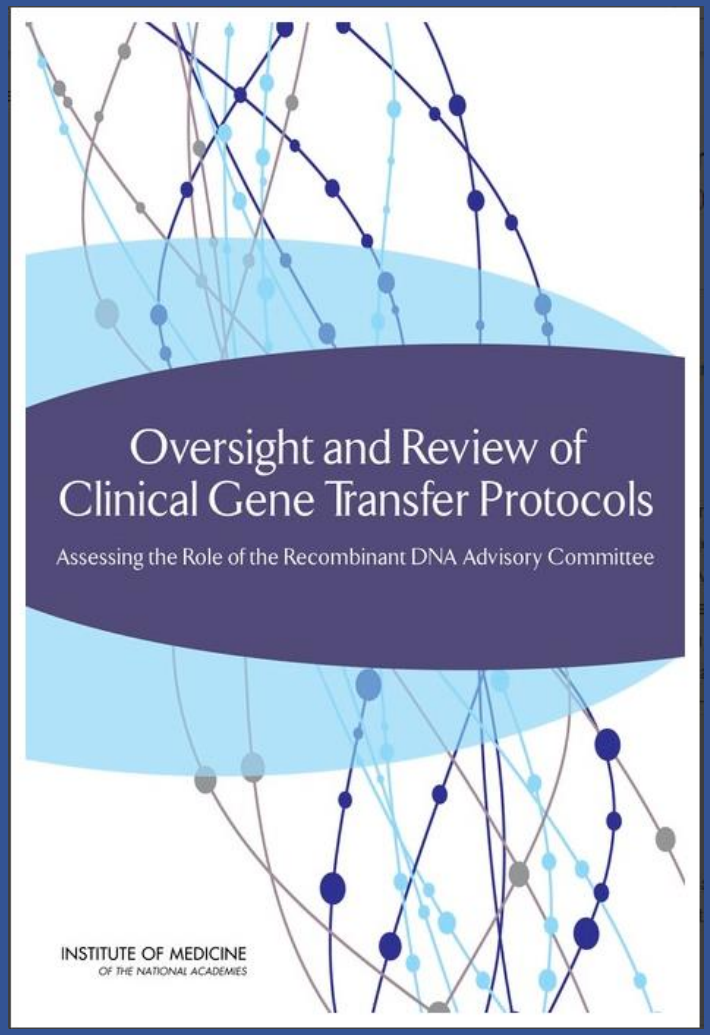
National advisory body established in 1974

- Provides advice and recommendations to the NIH Director on all aspects of basic or clinical recombinant or synthetic nucleic acid research
- Proposes changes to the *NIH Guidelines* as needed
- Provides a public forum for policy development through the discussion of biosafety, clinical, and ethical issues that arise from such research

RAC Review of Human Gene Transfer Research

- Provides a unique open and transparent forum to tackle ongoing scientific, safety, and ethical issues with the research community and public
  - Allows the field to advance and grow with the benefit of shared learning
  - Enhances safety and efficiency of the research
- Any gene editing research that falls within the scope of the *NIH Guidelines* would receive the same oversight as other gene transfer approaches

Institute Of Medicine Study



- NIH requested an independent review and assessment to
  - "Determine if gene transfer research raises issues of concern that warrant extra oversight by the RAC of individual clinical trial protocols involving gene transfer techniques"
  - "Recommend criteria to guide when the RAC should review this research"

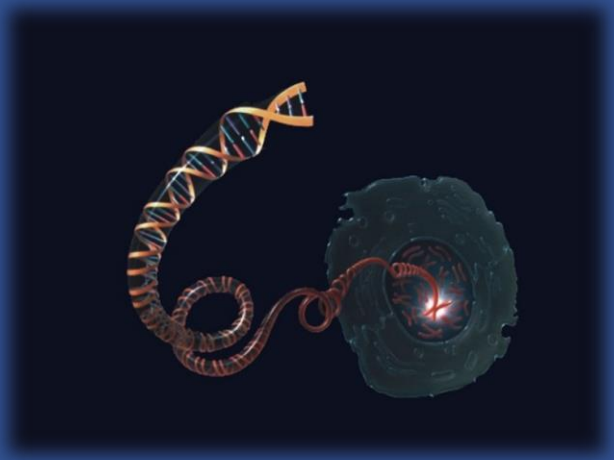
April 2016 Changes to RAC Review of Human Gene Transfer Research

- As science evolves, NIH strives for parallel evolution of our policies, the *NIH Guidelines* and the roles of the RAC to help ensure oversight of research is commensurate with risk involved

- ***Implementation of IOM Recommendation-*** As gene therapy field is maturing, in-depth RAC review and public discussion will be limited to exceptional cases
  - RAC continues to provide a public forum for discussion of scientific, safety and ethical issues associated with novel gene transfer trials and emerging technologies with unknown risks

RAC Review of Gene Editing Research

- Several protocols involving the use of somatic gene editing approaches have been reviewed by the RAC:
  - Zinc Finger Nucleases
    - Disruption of CCR5 to confer HIV resistance
    - Introduction of genes to correct hemophilia B and mucopolysaccharidosis I
  - CRISPR/Cas9
    - First-in-human use reviewed at June 2016 meeting
    - Deletion of endogenous T cell receptors (TCR) and PD-1 in autologous T cells also modified to express TCRs targeting tumor cells



CRISPR/Cas9 Protocol Review

- RAC Members raised important scientific and ethical issues such as
  - The desirability of sensitive assays to detect translocations that could possibly result from the simultaneous editing of three different loci by the CRISPR/Cas9 system
  - Addition of clarification that this is first-in-human use of CRISPR/Cas9 in informed consent documents
  - Close attention to possible conflicts of interest
- Forums such as the RAC provide an opportunity for open and transparent discussion of unique issues posed by such ground-breaking clinical trial protocols

In utero Gene Therapy/Gene Editing

Regulatory and Policy Requirements Governing In utero Gene Editing Research

- FDA
  - Regulations on Investigational New Drug Applications (21 CFR 312)
  - Review of research in which a human embryo is intentionally created or modified to include a heritable genetic modification is prohibited (Public Law 114-113)
- HHS Regulations on the Protection of Human Subjects (45 CFR 46, Subparts A and B)
- *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*
  - Effectively prohibit germline gene transfer [amended in 1986]
  - Amended in 1999 to address *in utero* gene transfer research

Key Requirements of Subpart B 45 CFR 46.204

- For research focused on the fetus (and not also the pregnant woman):
  - Data must be available from preclinical studies to assess risks to pregnant women and fetuses
  - Interventions or procedures must be designed to benefit the fetus
  - Any risk is least possible for achieving objectives
  - Maternal and paternal consent (if possible)

NIH Guidelines – Germ line Alterations

"The NIH will not at present entertain proposals for germ line alterations . . .. Germ line alteration involves a specific attempt to introduce genetic changes into the germ (reproductive) cells of an individual, with the aim of changing the set of genes passed on to the individual's offspring."

> *Appendix M, third paragraph* (statement first published in the NIH Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols, September 29, 1986)

NIH Guidelines – in utero Gene Therapy

". . . at present, it is premature to undertake any *in utero* gene transfer clinical trial. Significant additional preclinical and clinical studies … are required before a human *in utero* gene transfer protocol can proceed ... [A] more thorough understanding of the development of human organ systems … is needed to better define the potential efficacy and risks of human *in utero* gene transfer. Prerequisites for considering any specific human *in utero* gene transfer procedure include an understanding of the pathophysiology of the candidate disease and a demonstrable advantage to the *in utero* approach. Once the above criteria are met, the NIH would be willing to consider well rationalized human *in utero* gene transfer clinical trials.

Appendix M, fourth paragraph, incorporated in 1999

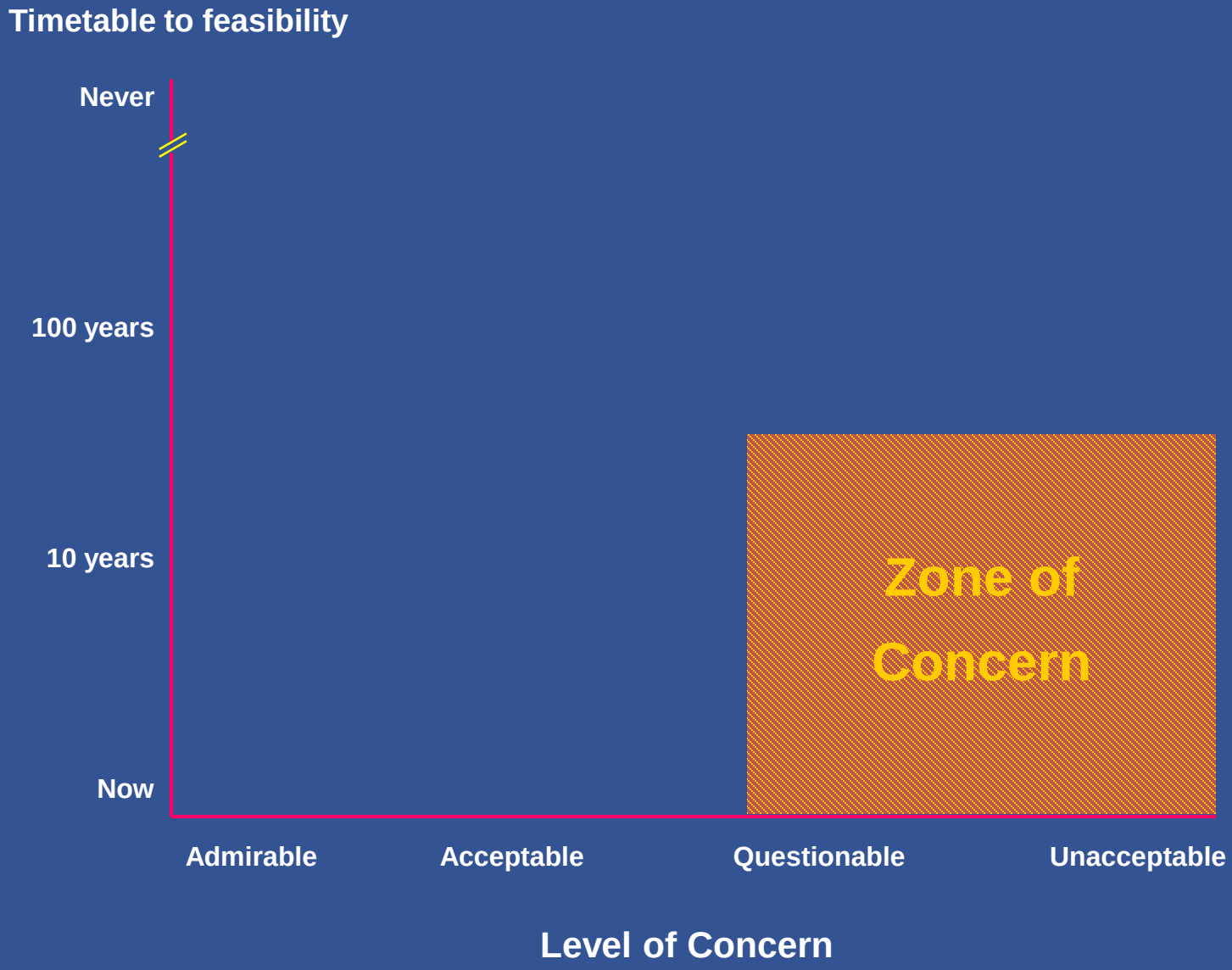
NIH Gene Therapy Policy Conference
Prenatal Gene Transfer:
Scientific, Medical and Ethical Issues

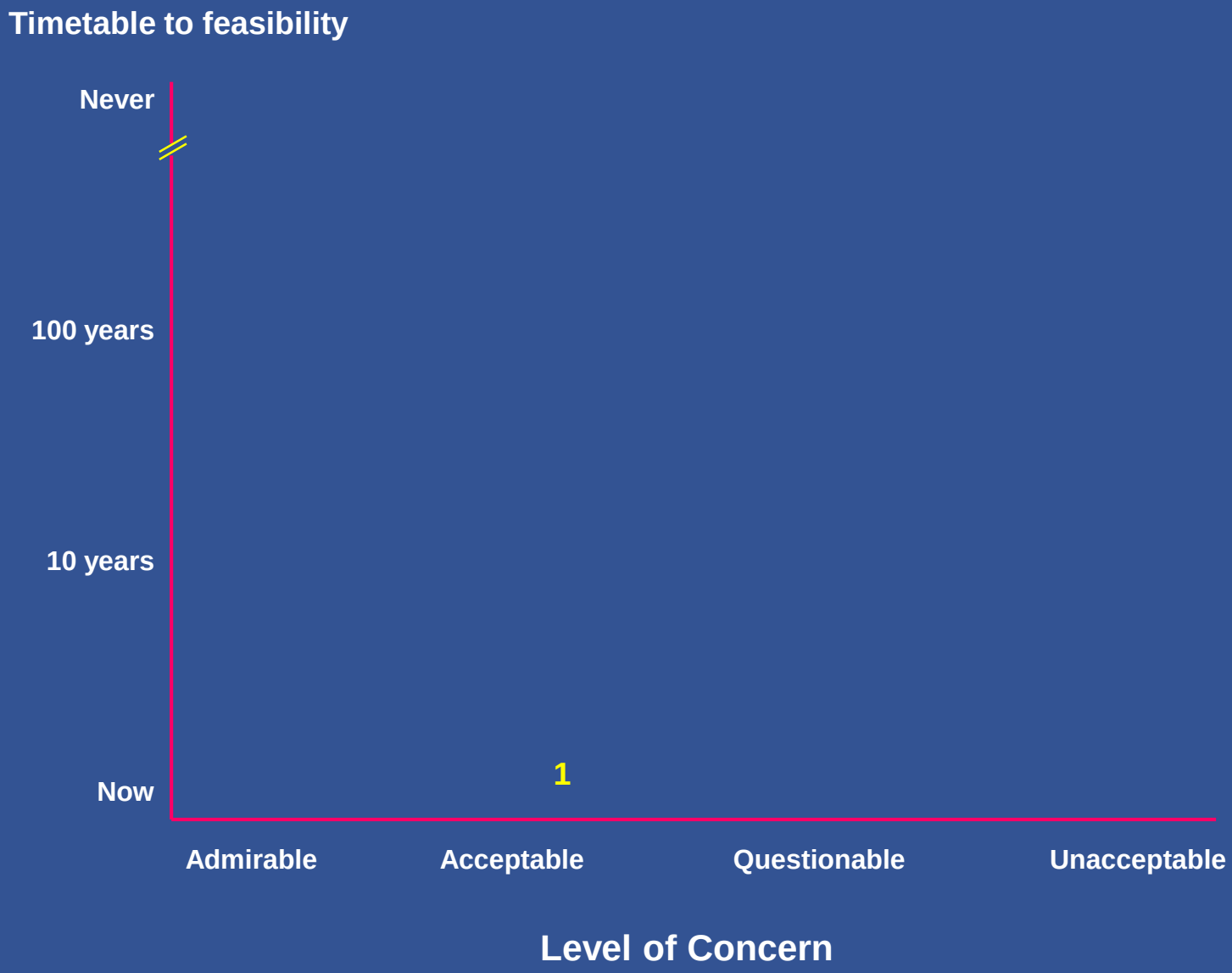
- Report issued in 1999 but conclusions remain useful
- Some issues addressed through general advancements in the gene transfer field
- Other issues remain
  - Scientific issues
    - Potential risks to fetus and pregnant women, effects on fetal development and immune response, appropriate disease candidates, germline alteration
  - Ethical issues
    - Inadvertent germline modification, risk: benefit assessment, informed decision-making, equity of access

Key Questions in Considering Appropriateness of Fetal Research

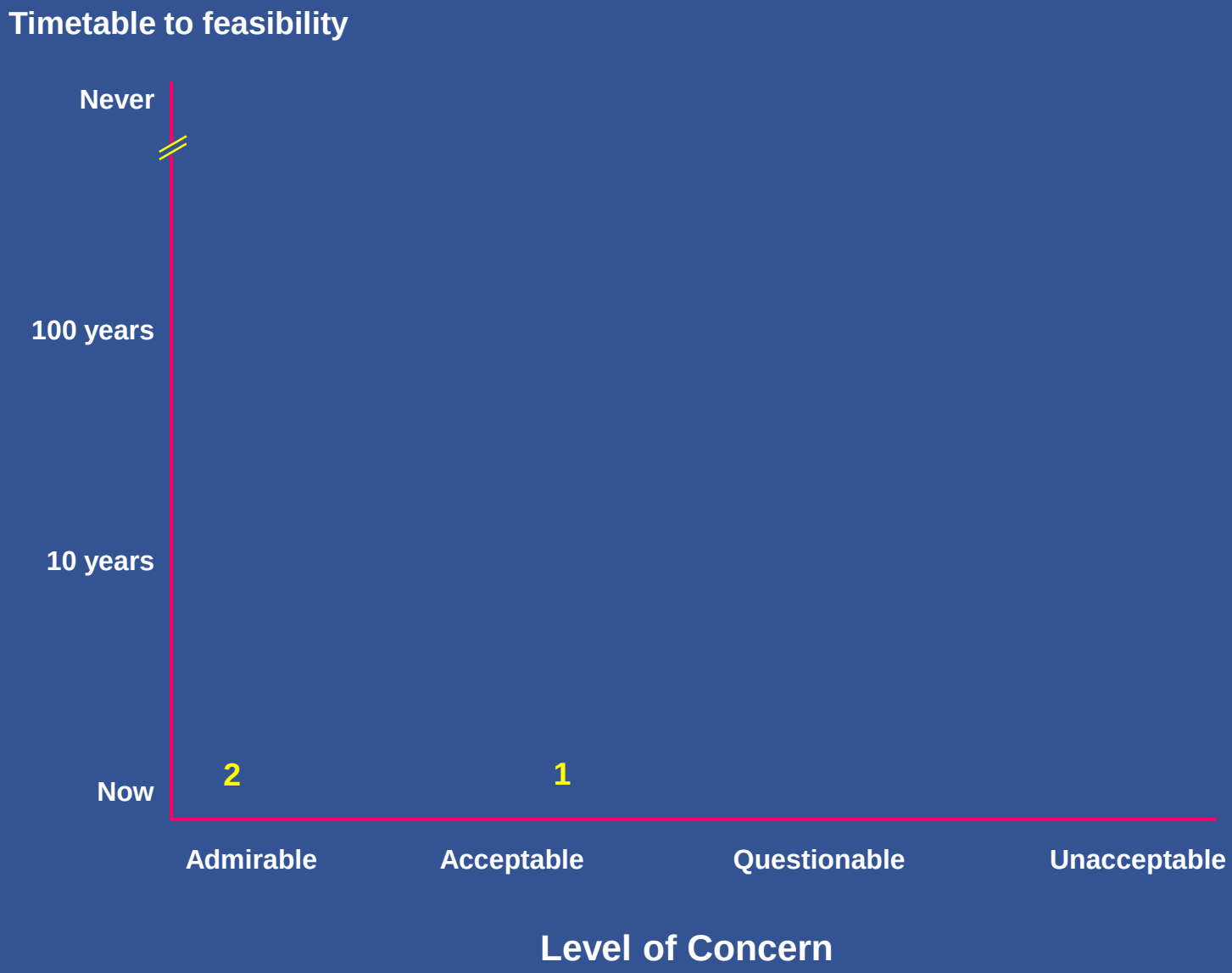
- Target of gene therapy/editing: somatic or germline cells?
- Reliability of vector to target only intended cells?
- For what purpose? Amelioration of disease, or enhancement of desired traits?

Other gene editing topics of interest?

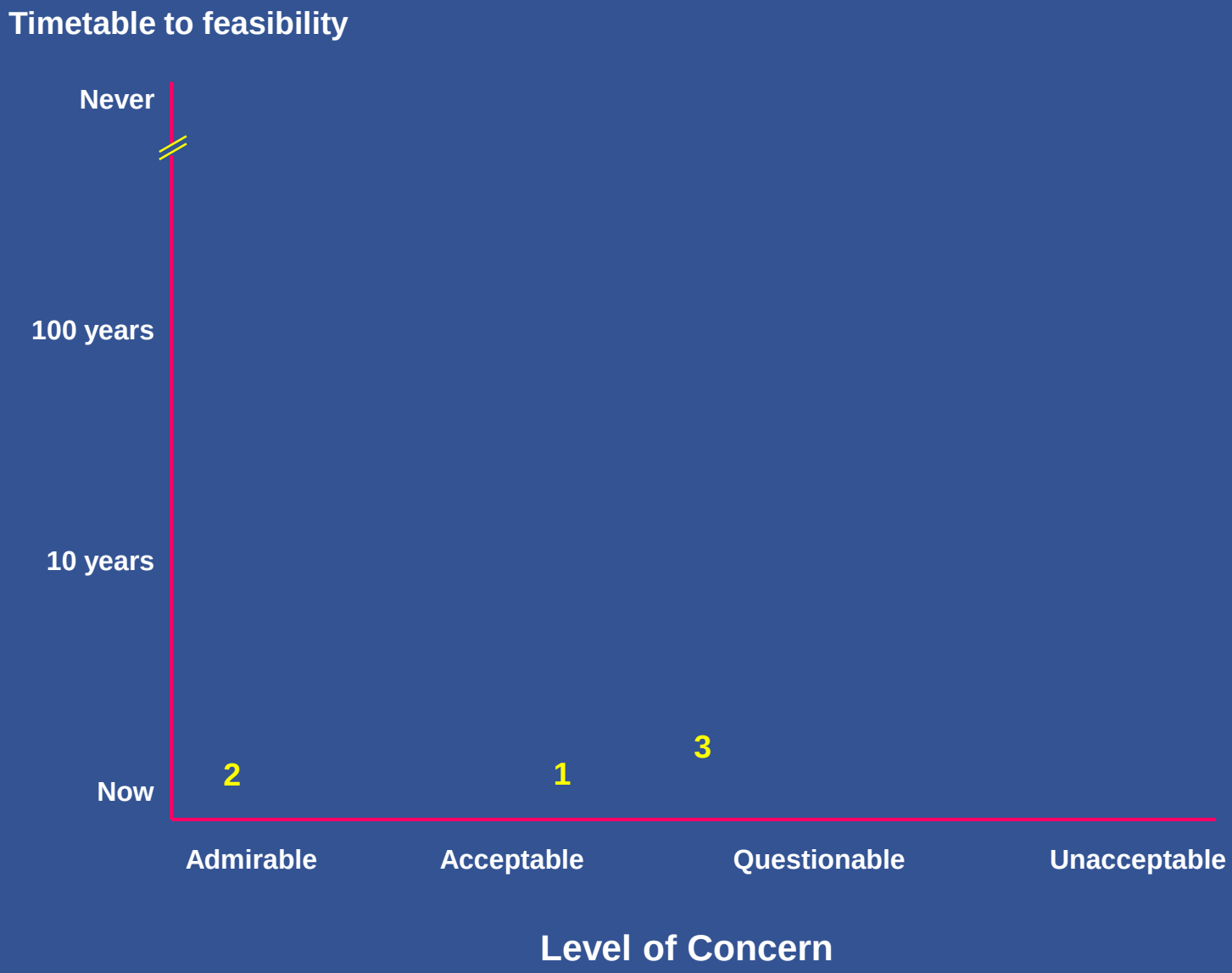

Timetable to feasibility
Never
100 years
10 years
Now
Zone of Concern
Admirable
Acceptable
Questionable
Unacceptable
Level of Concern



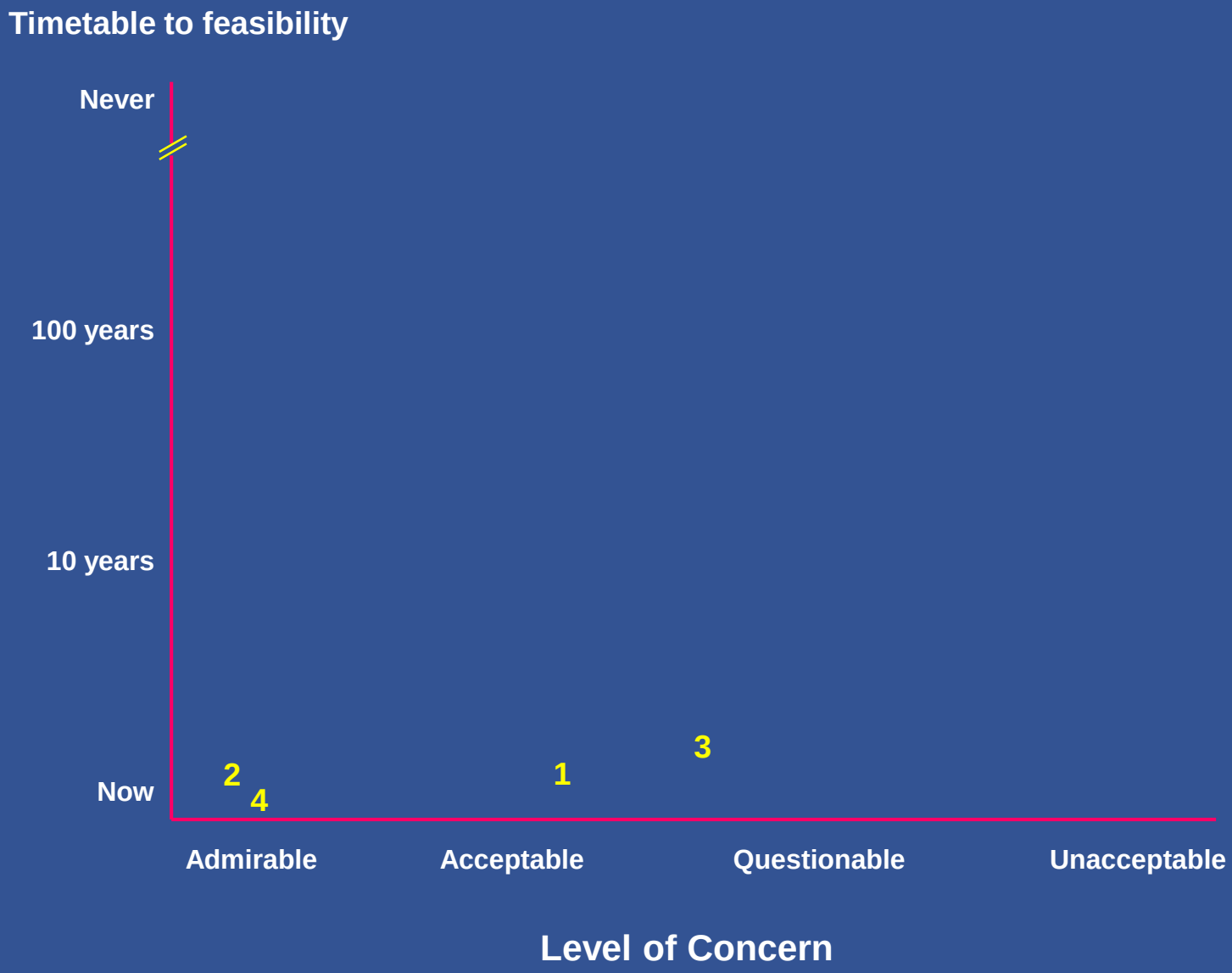
1. Hair coloring



2. Music lessons



3. Cosmetic surgery


Timetable to feasibility
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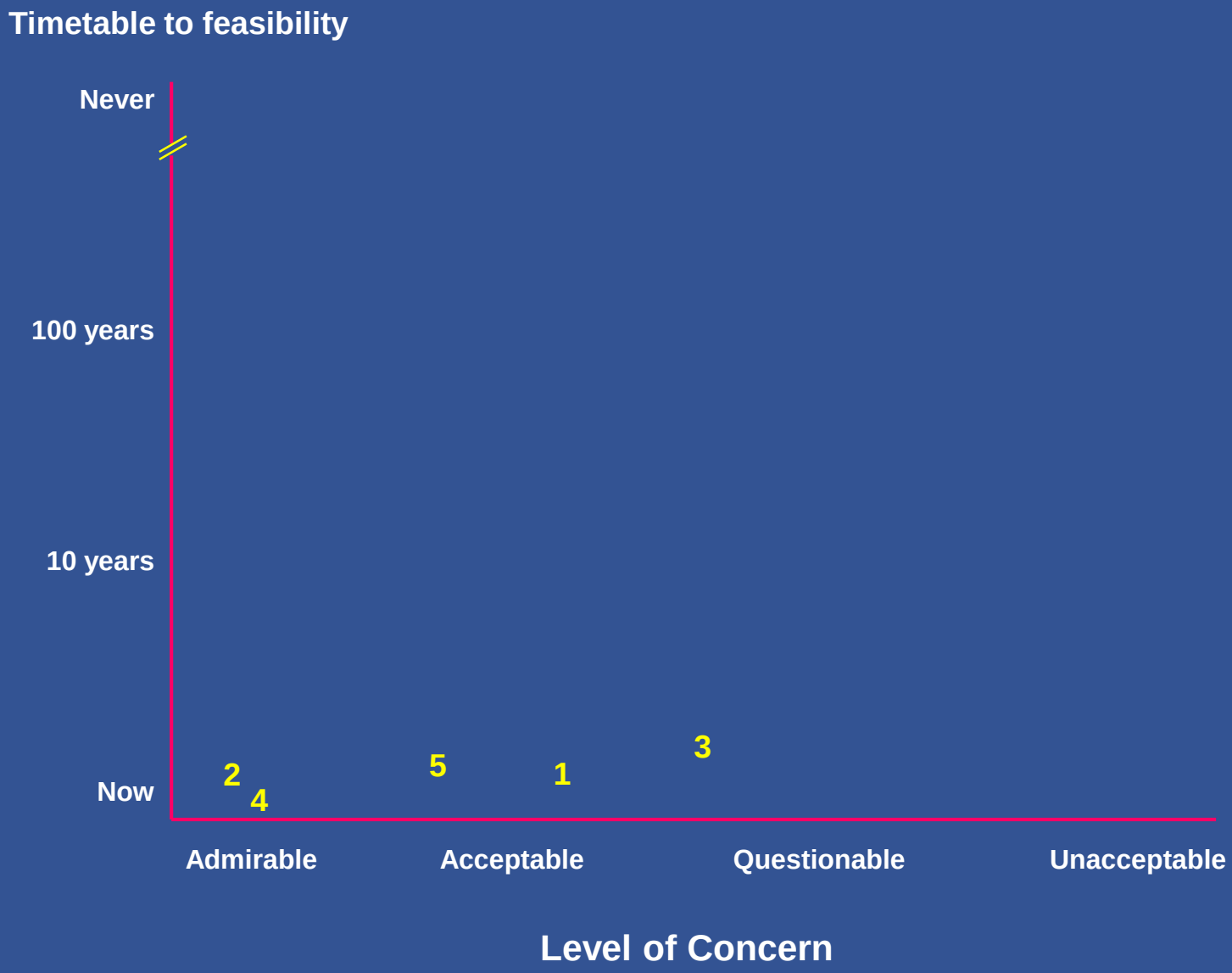
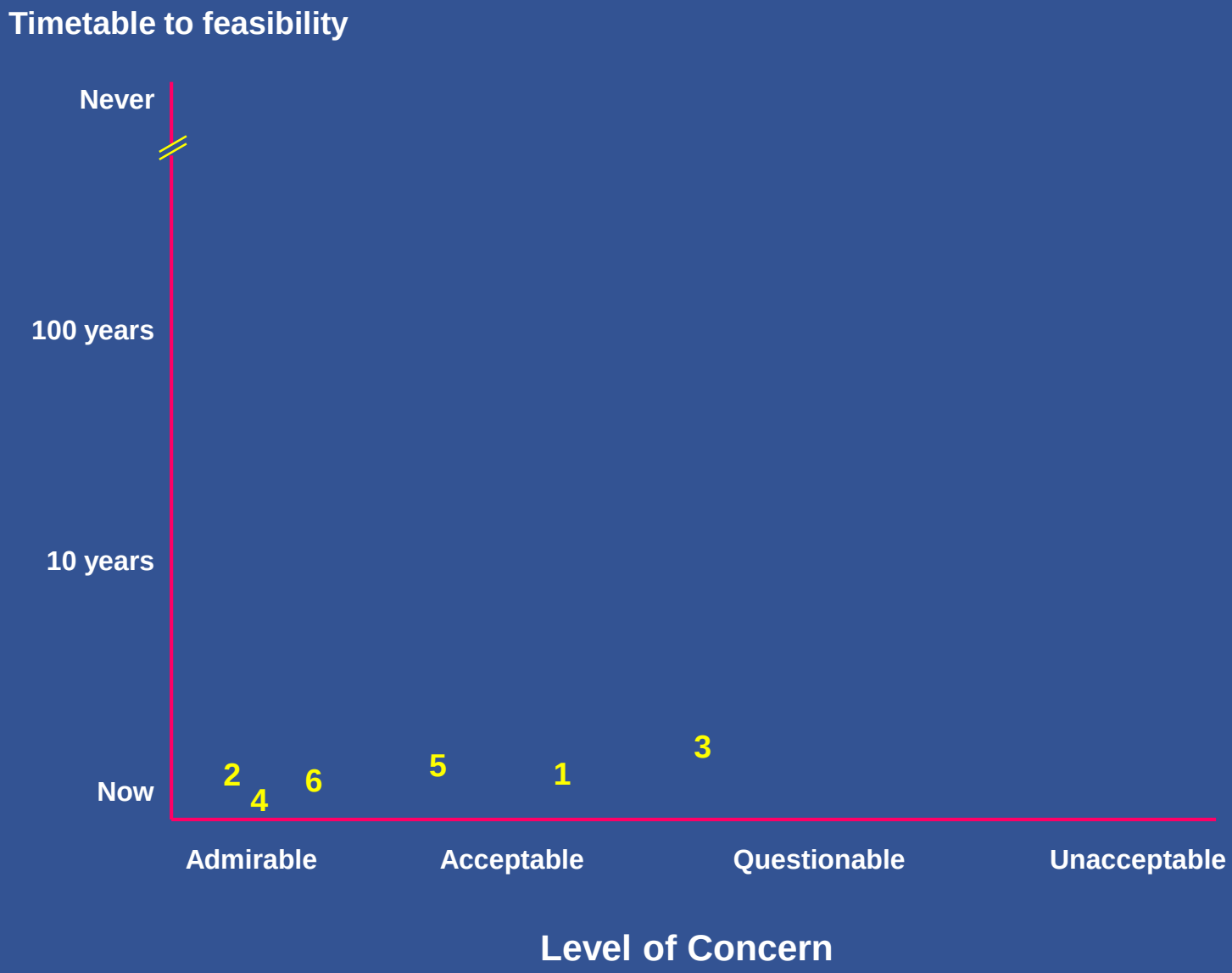
Admirable
Acceptable
Questionable
Unacceptable
Level of Concern

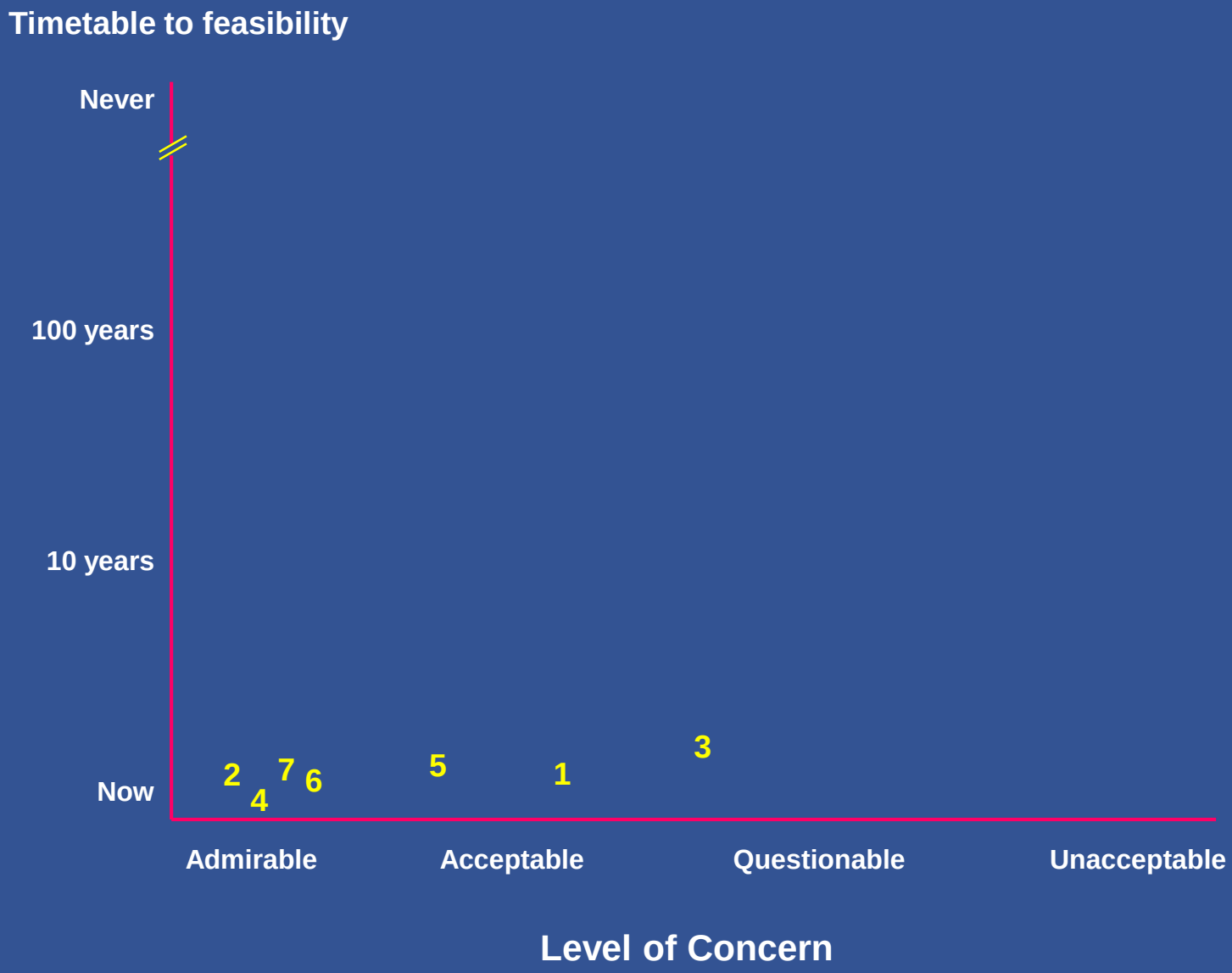
4. Exercise



5. Fluoridated water



6. Immunizations


Timetable to feasibility
Never
100 years
10 years
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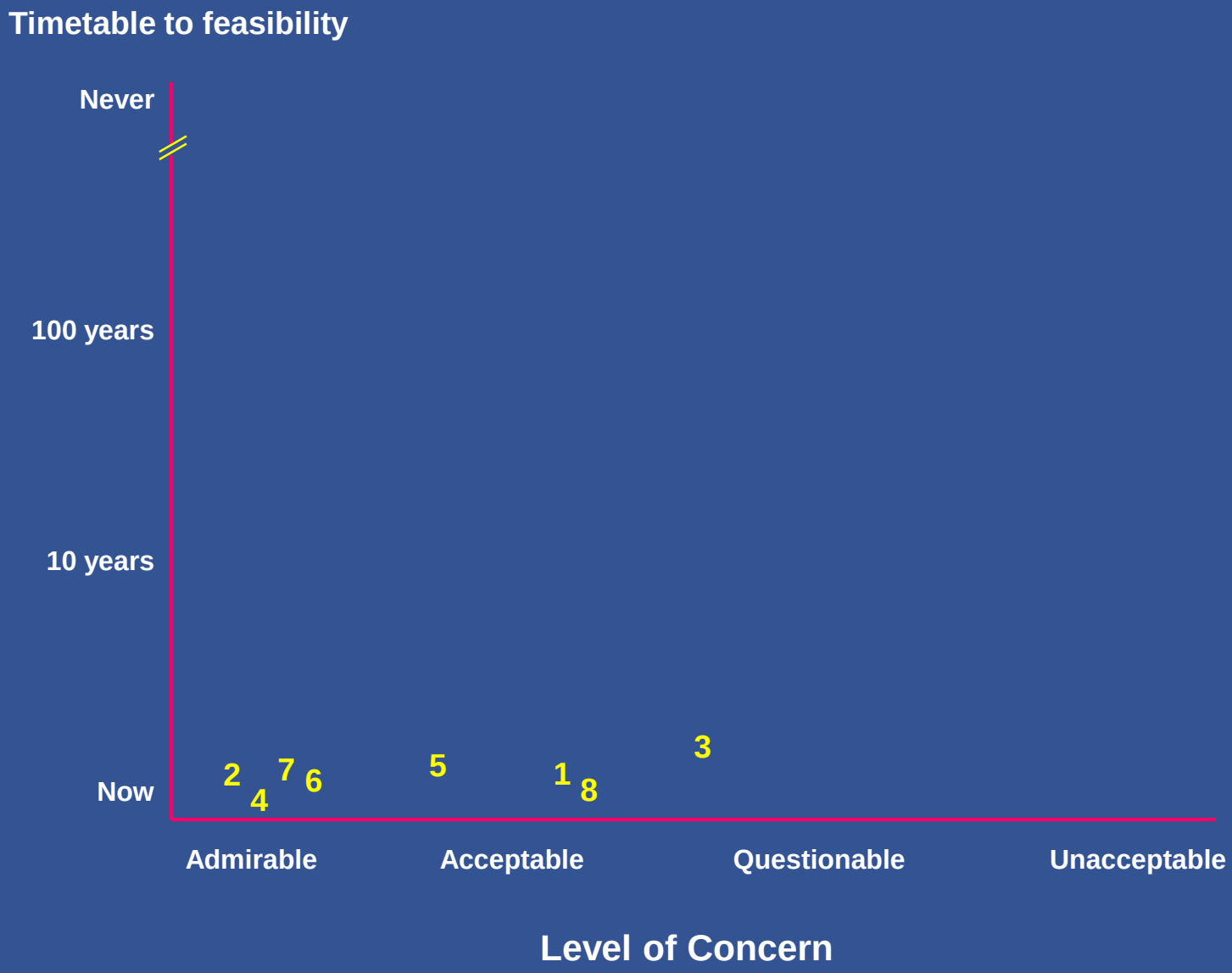
Admirable
Acceptable
Questionable
Unacceptable
Level of Concern

7. Prayer


Timetable to feasibility
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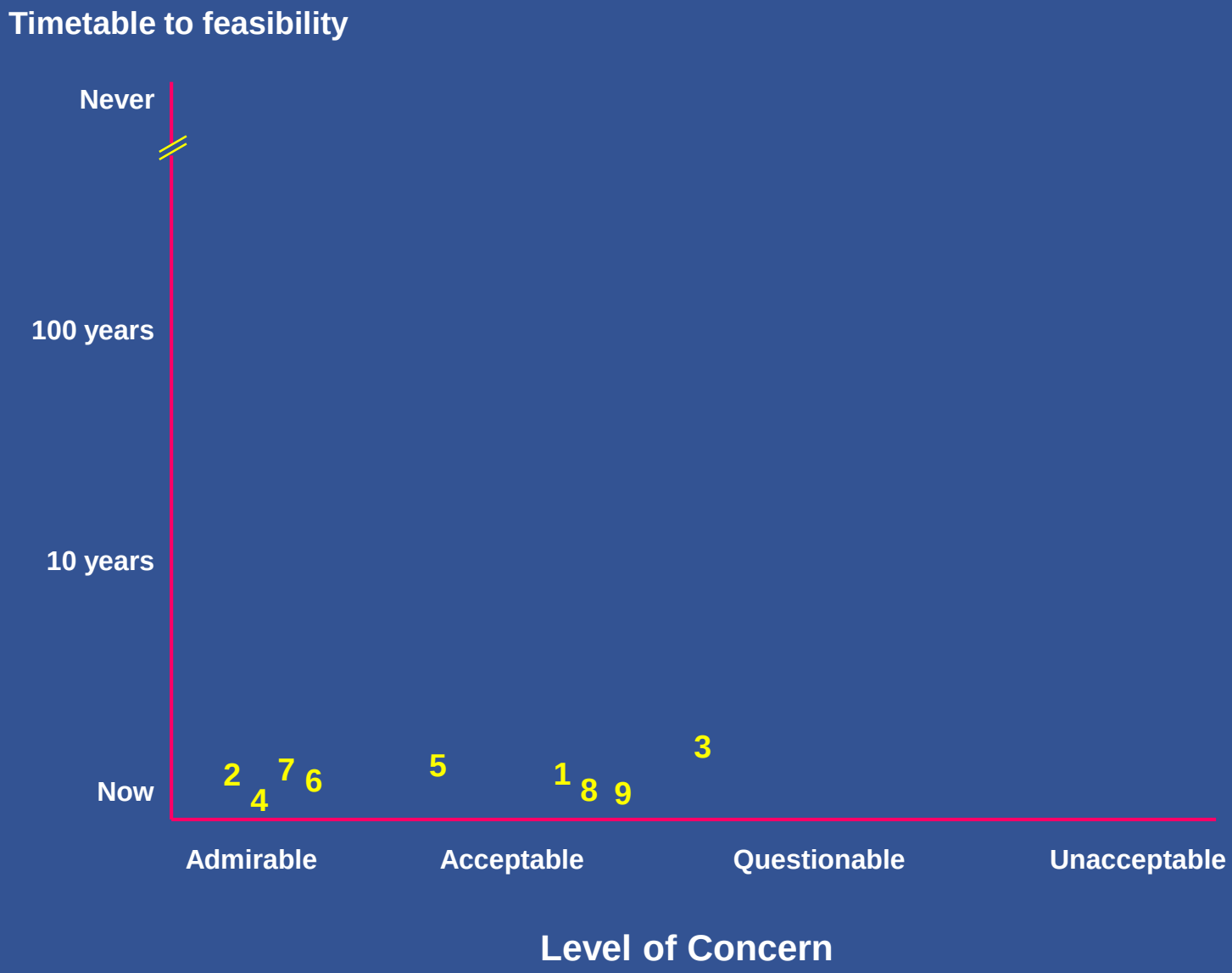
Questionable
Unacceptable
Level of Concern

8. Viagra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Admirable
Acceptable
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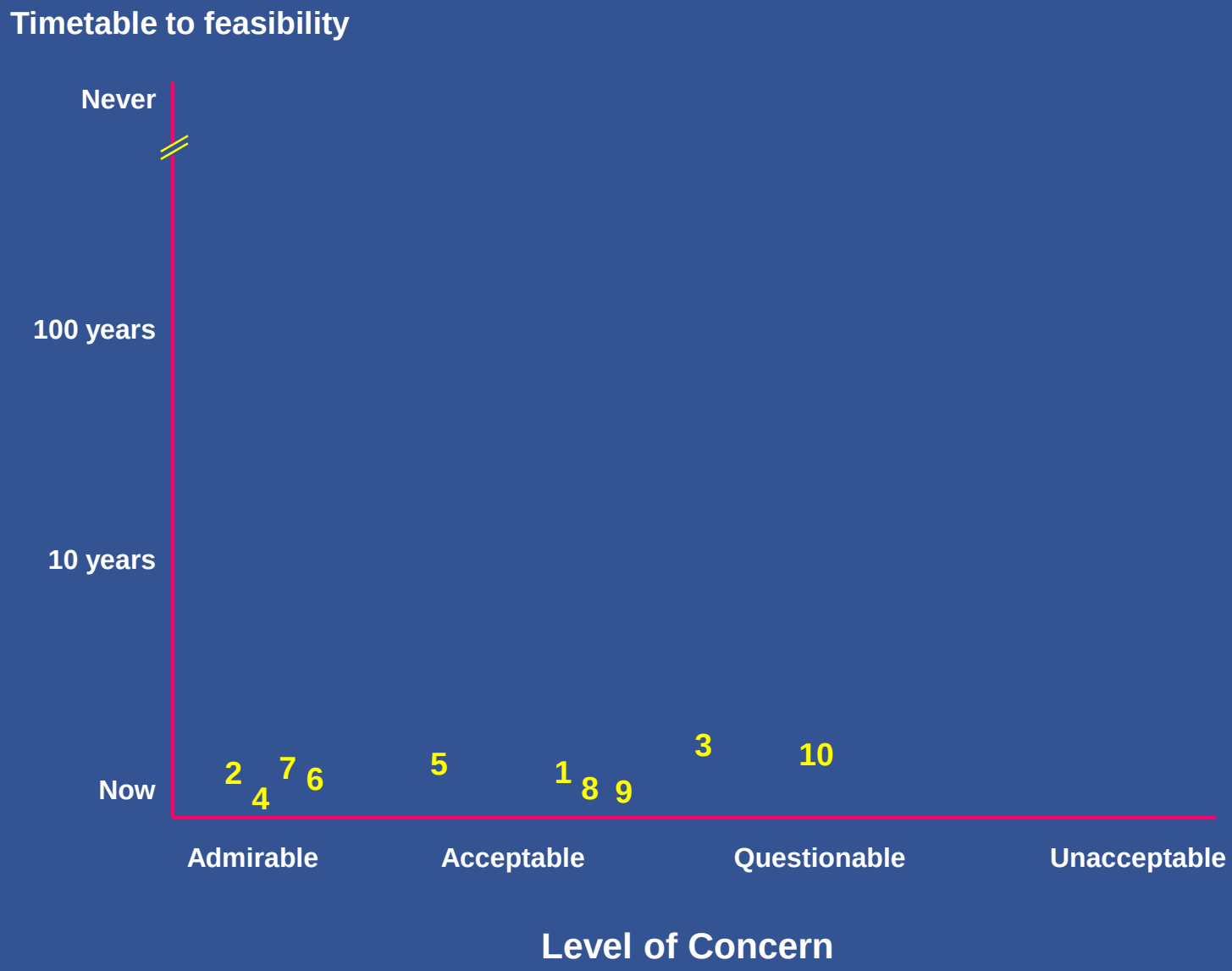
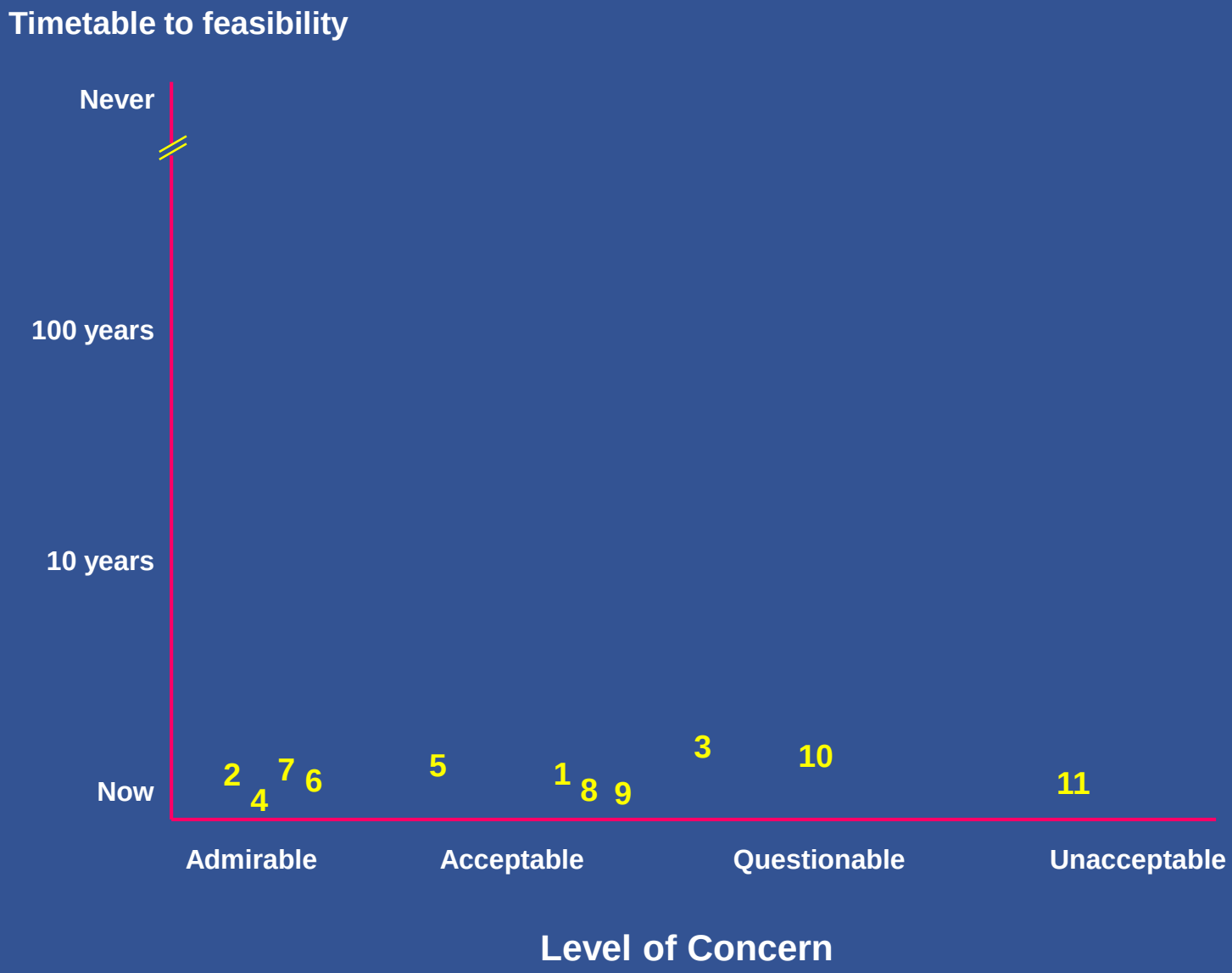
Level of Concern

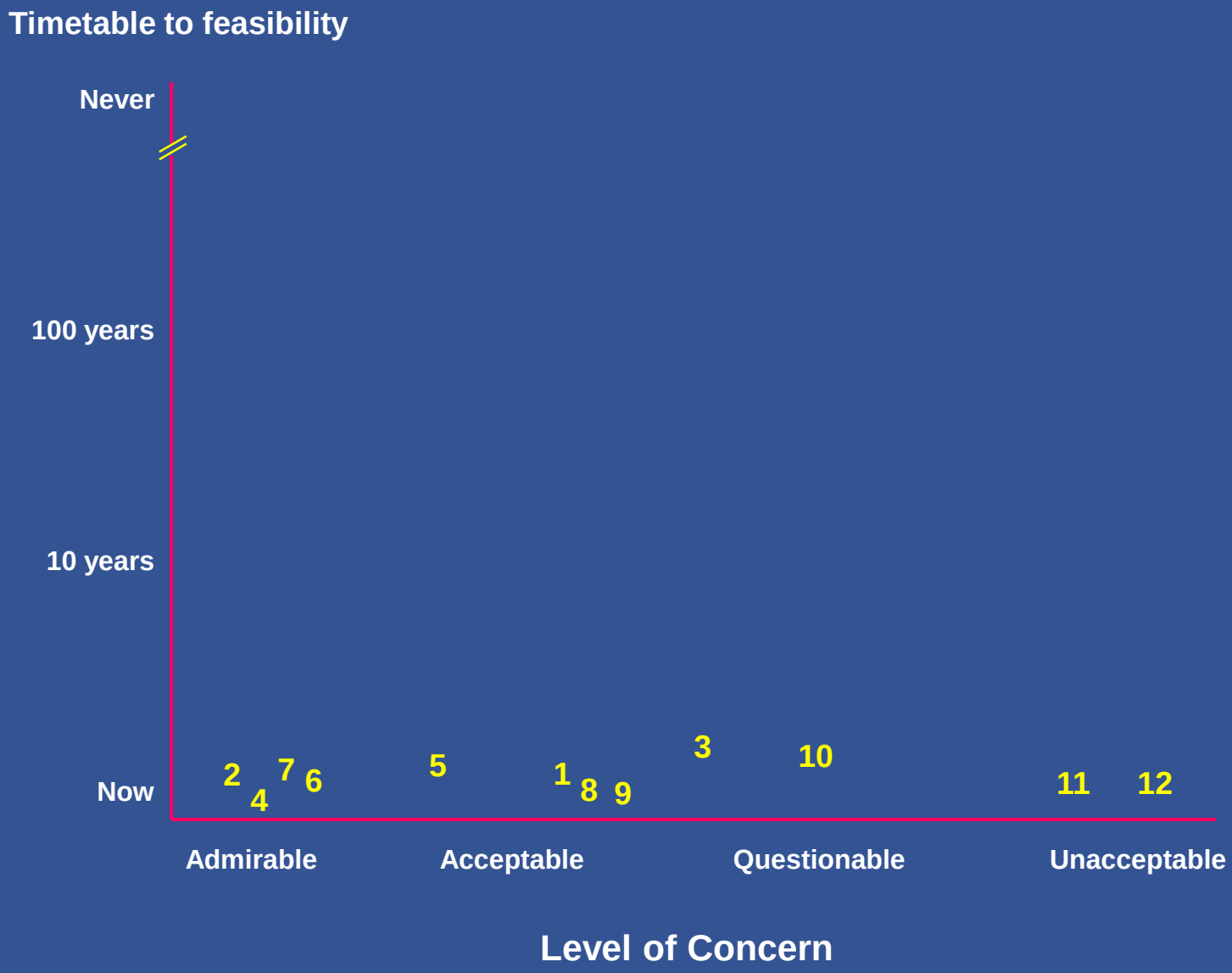
9. Ritalin



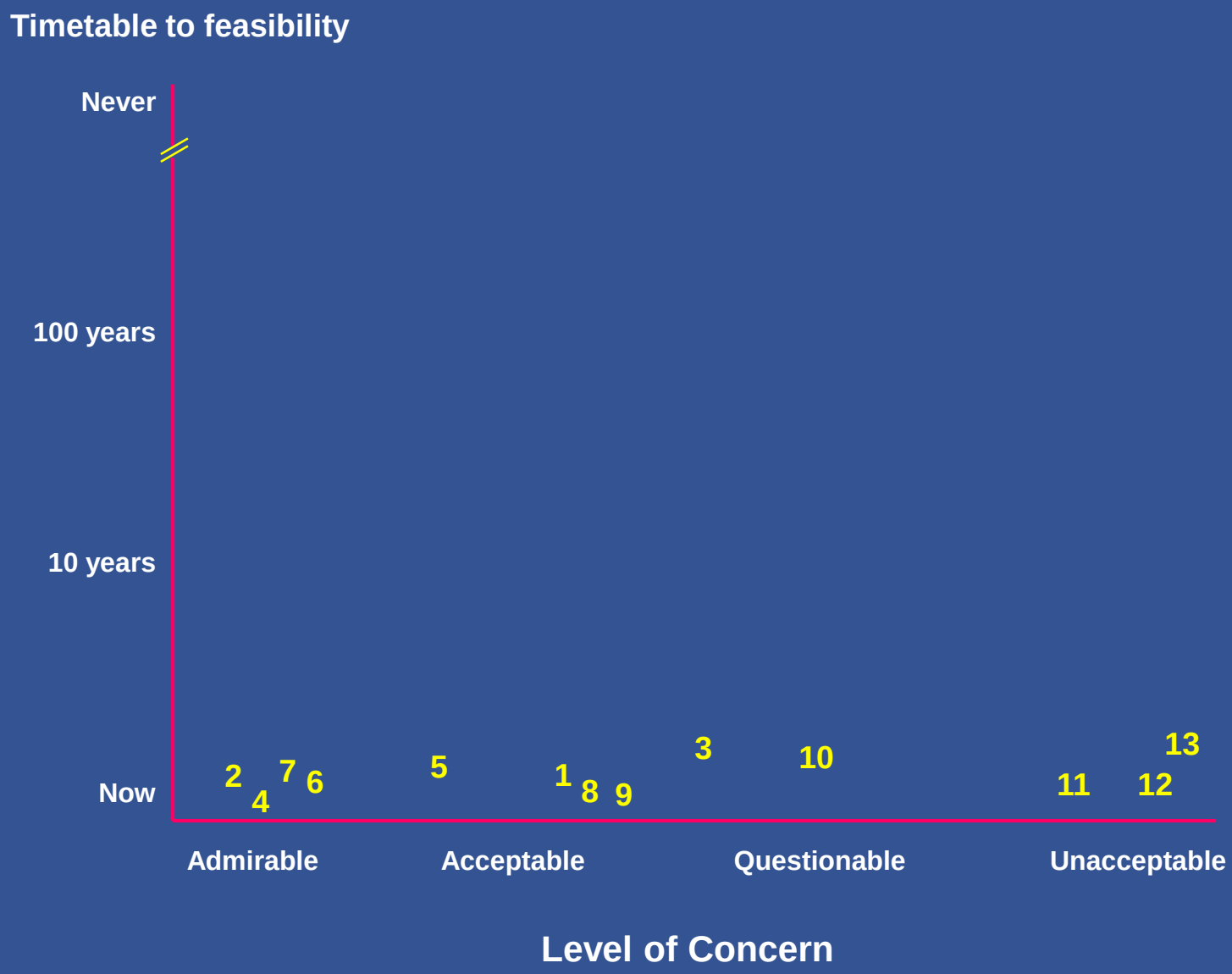
10. Mood altering drugs



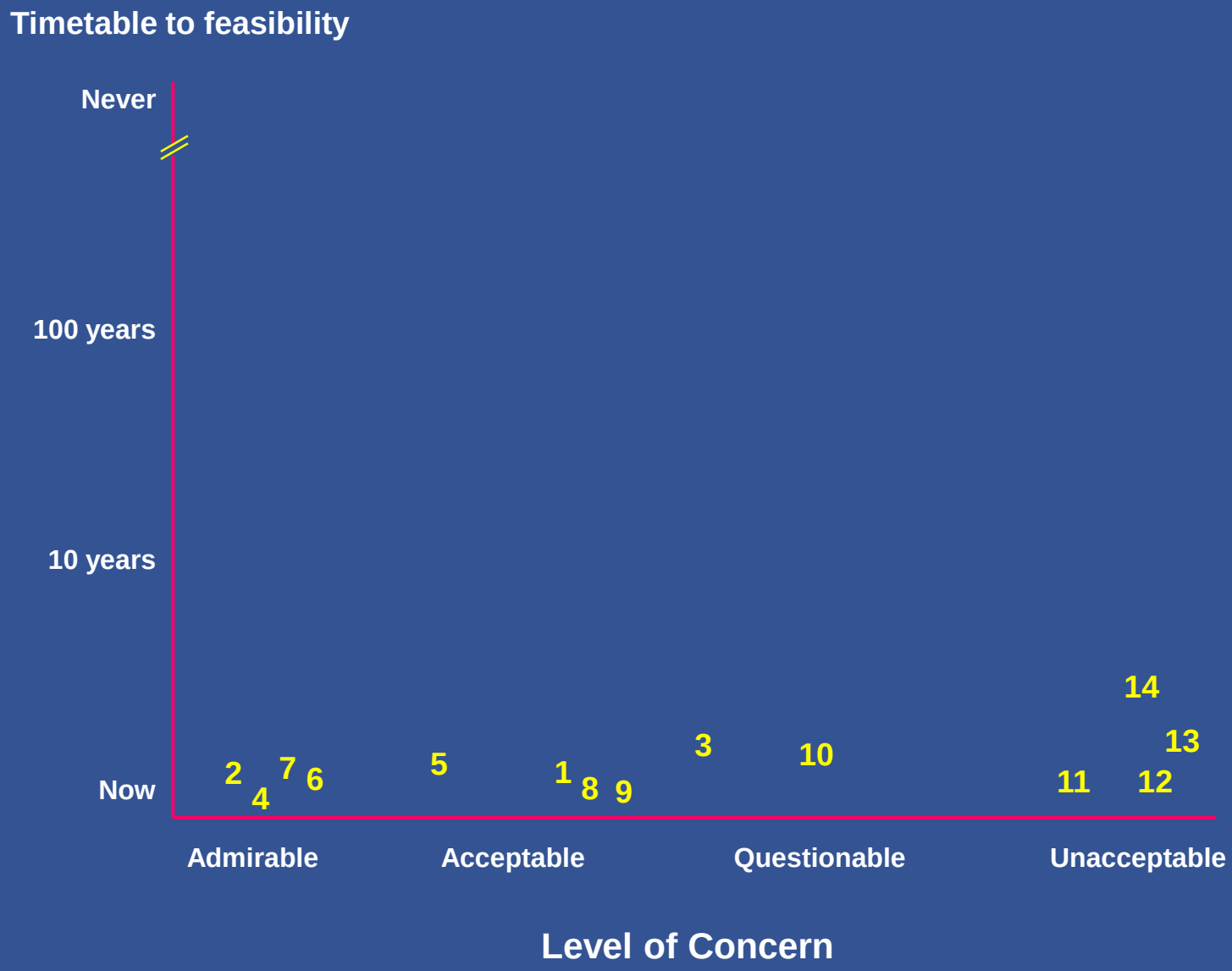
11. Recreational drugs



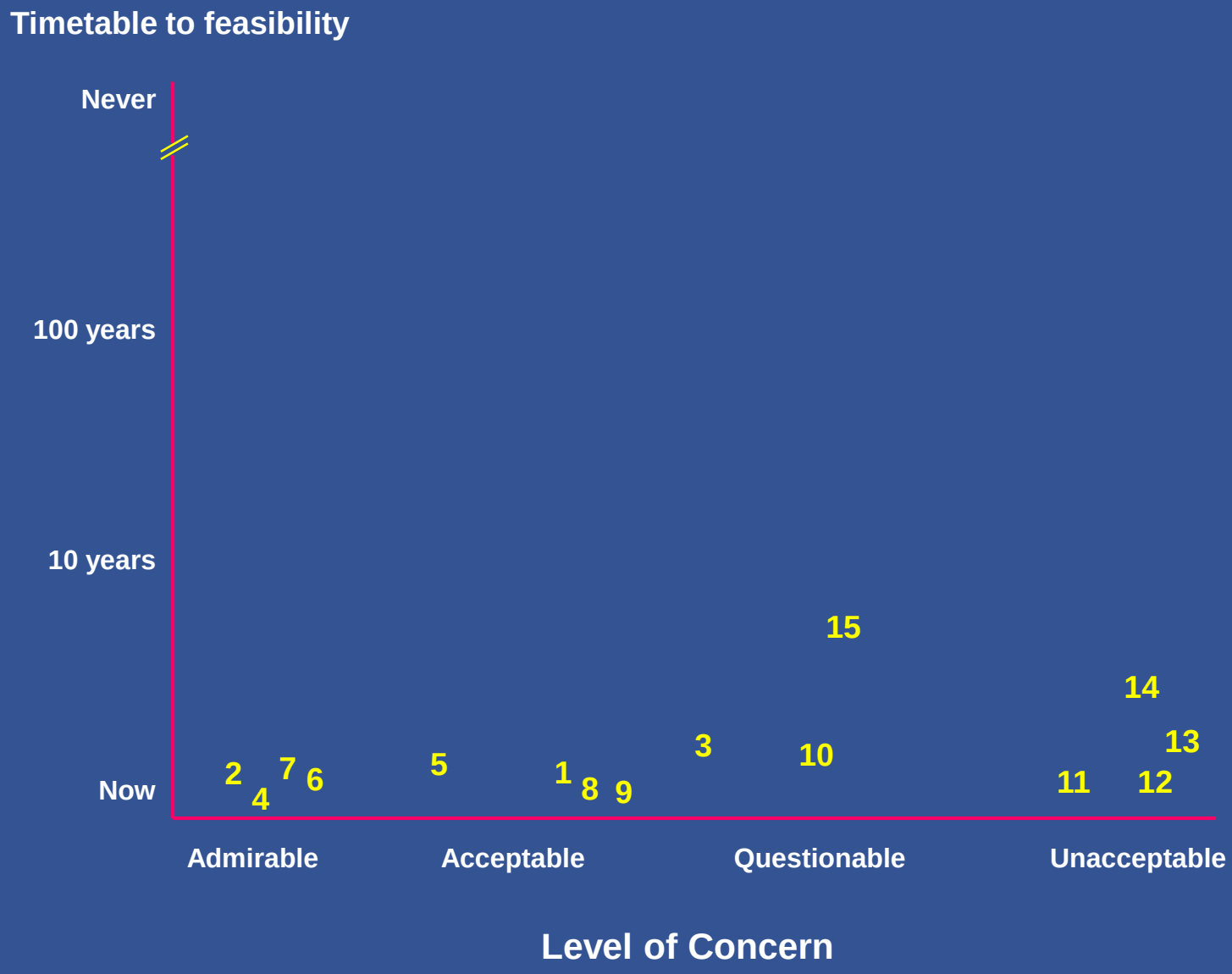
12. hGH for normal kids



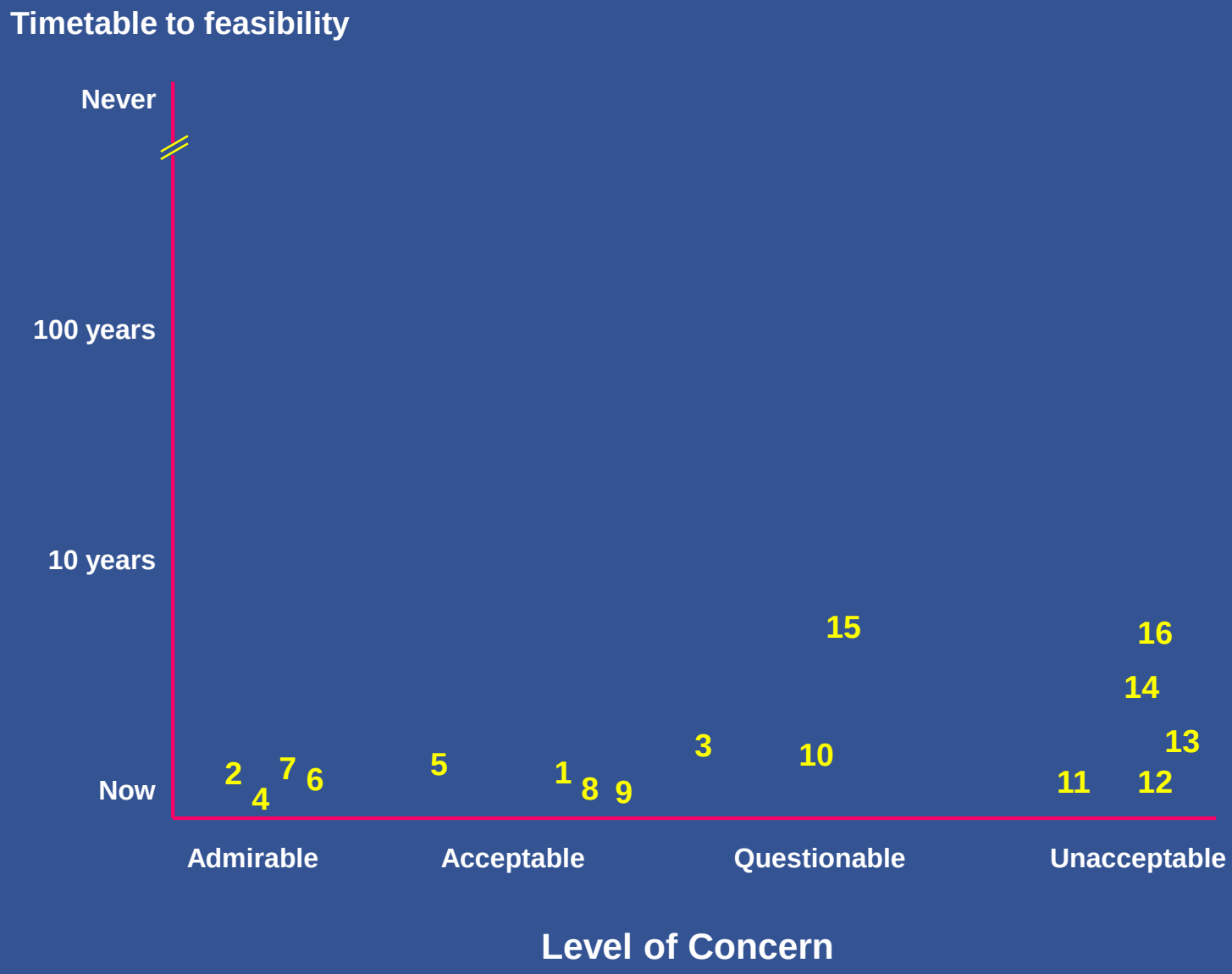
13. Epo for athletes



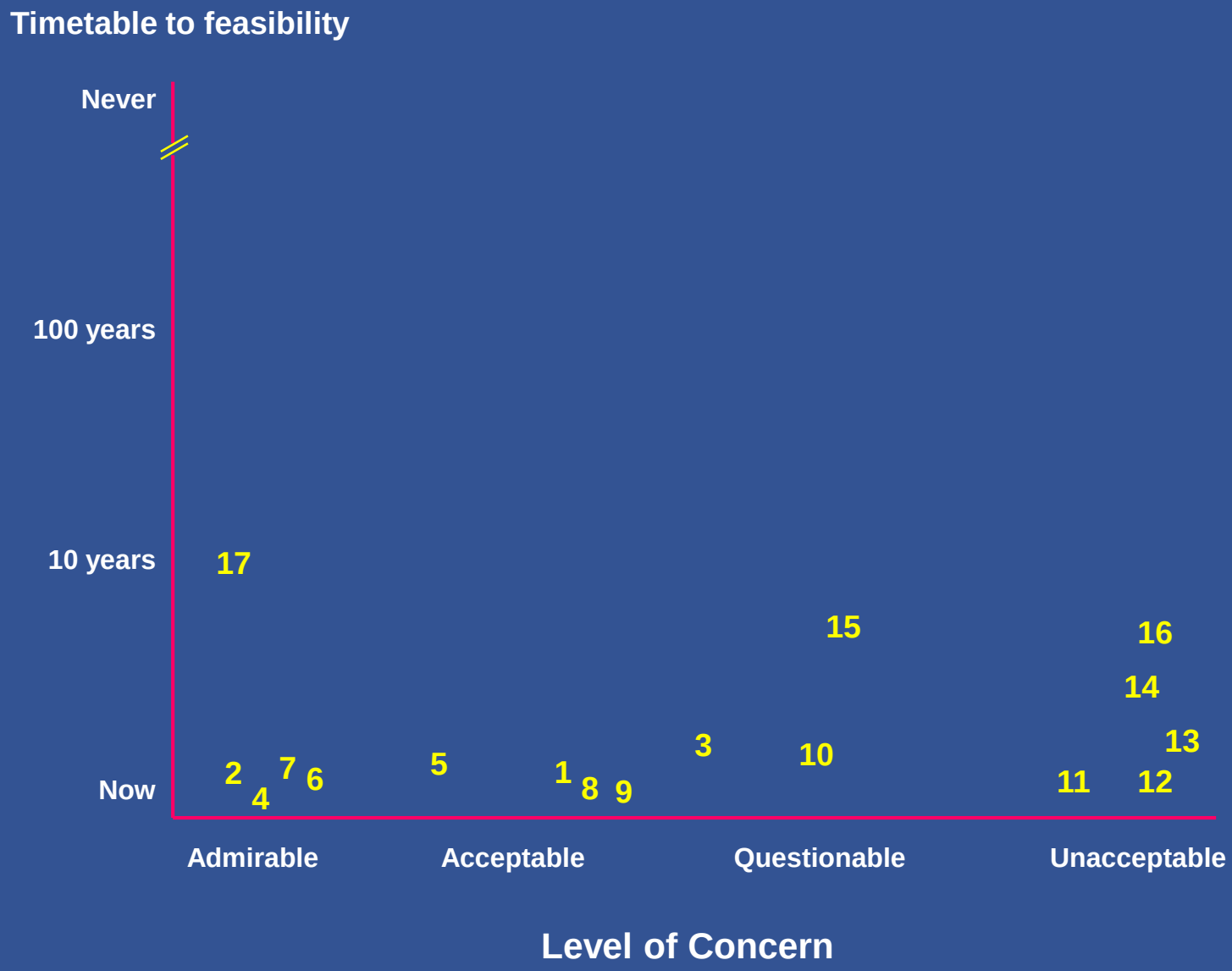
14. Sex selection



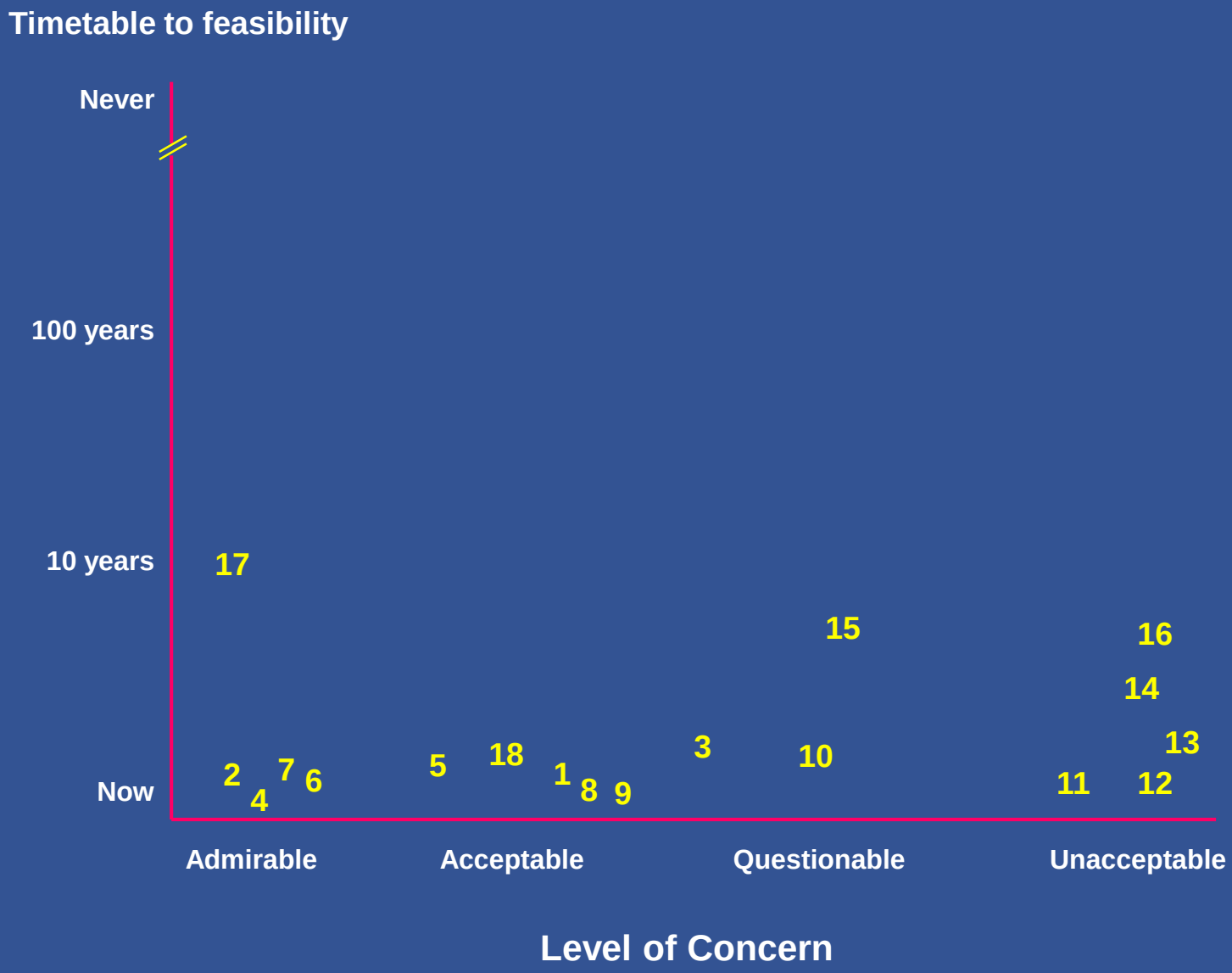
15. IGF-1 to prevent aging



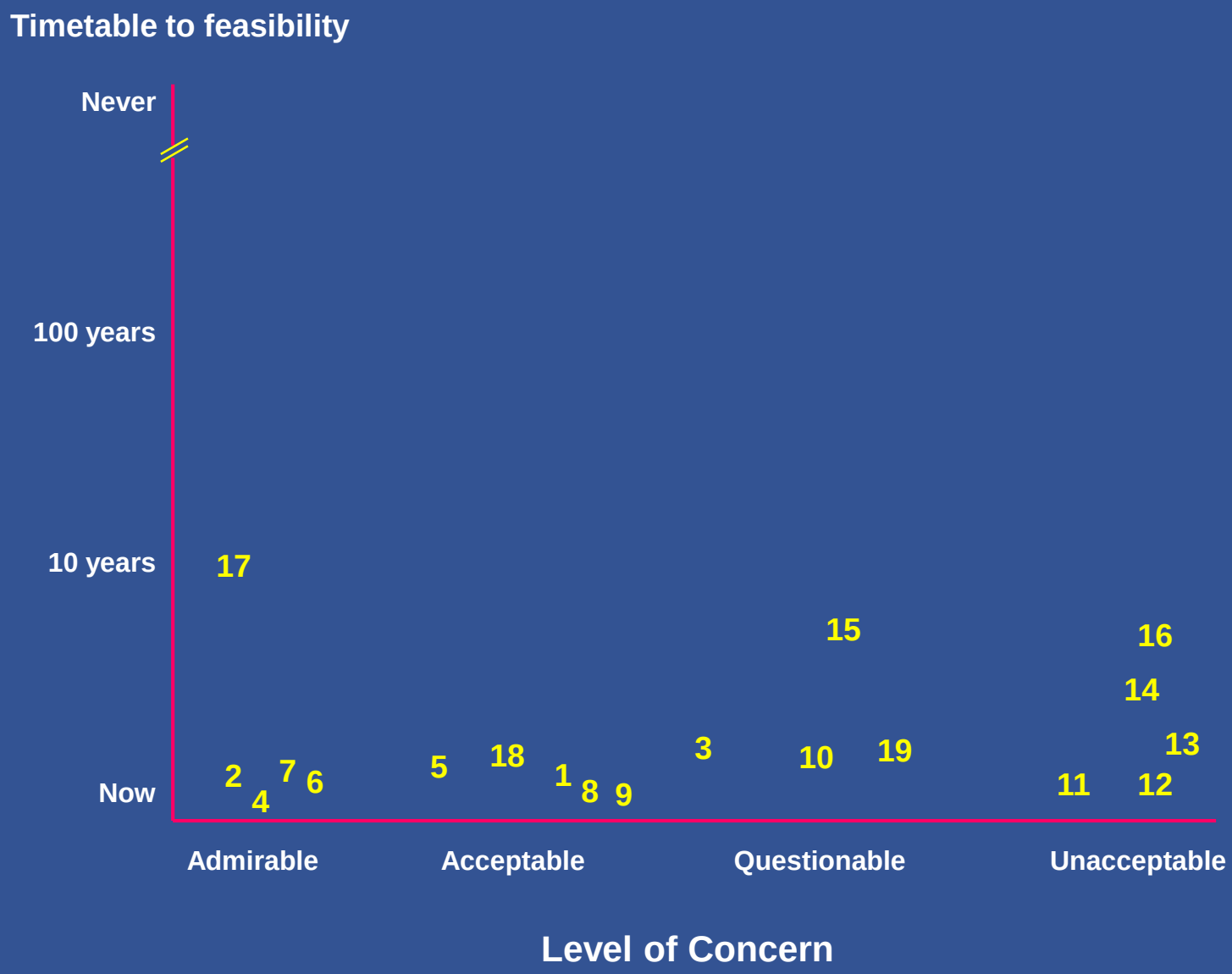
16. IGF-1 for athletes



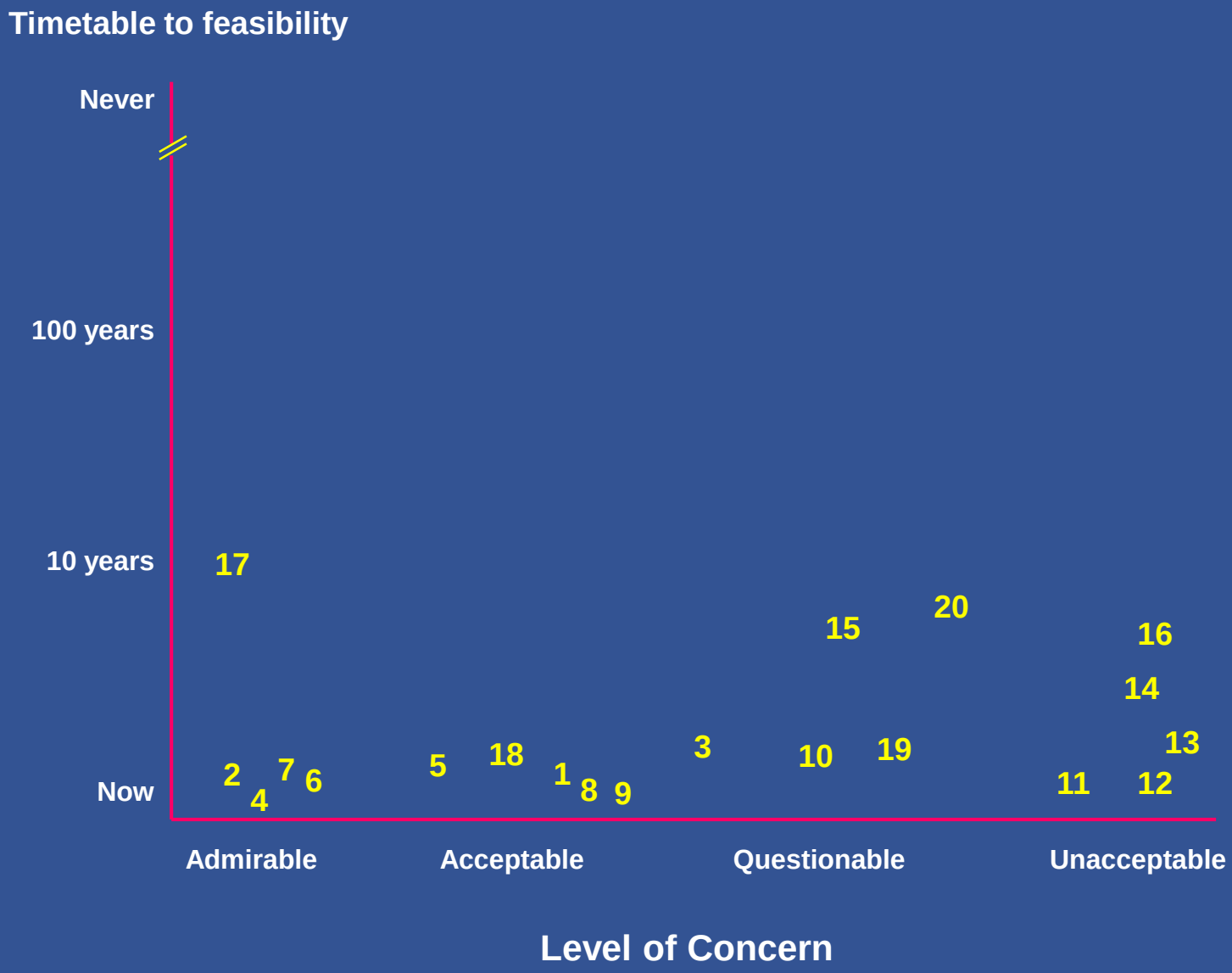
17. Individualized preventive medicine



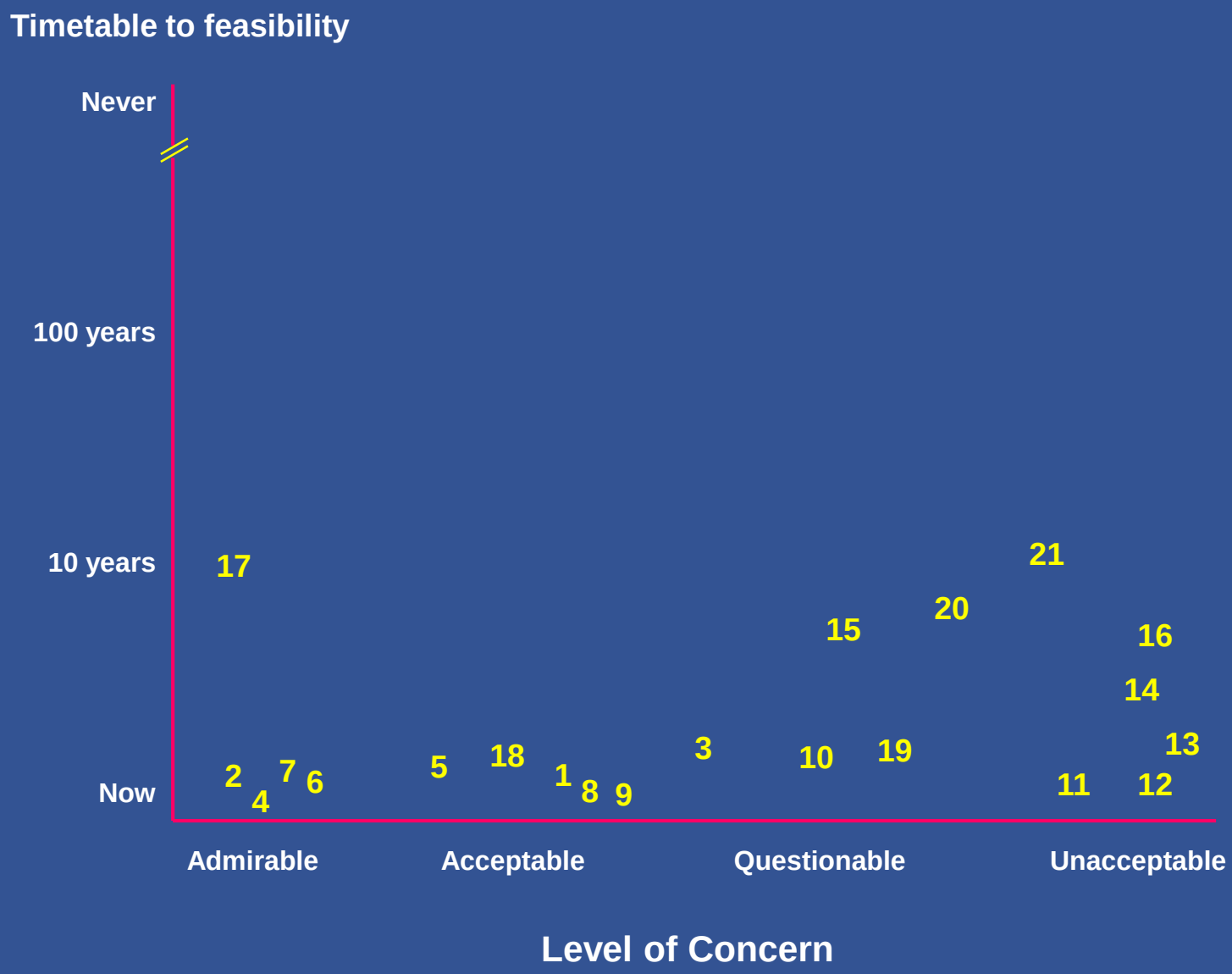
18. PGD for Tay Sachs disease



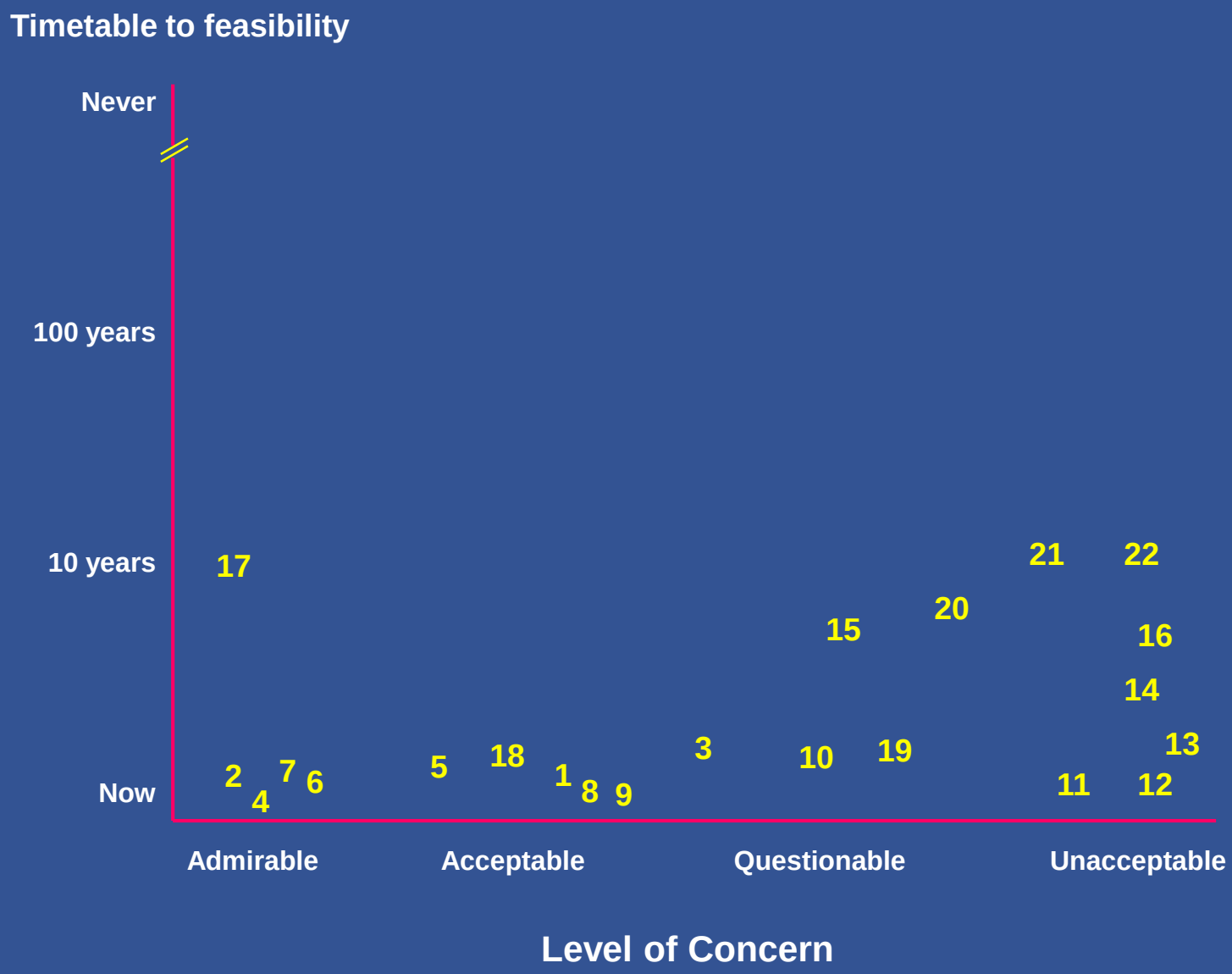
19. PGD for BRCA1



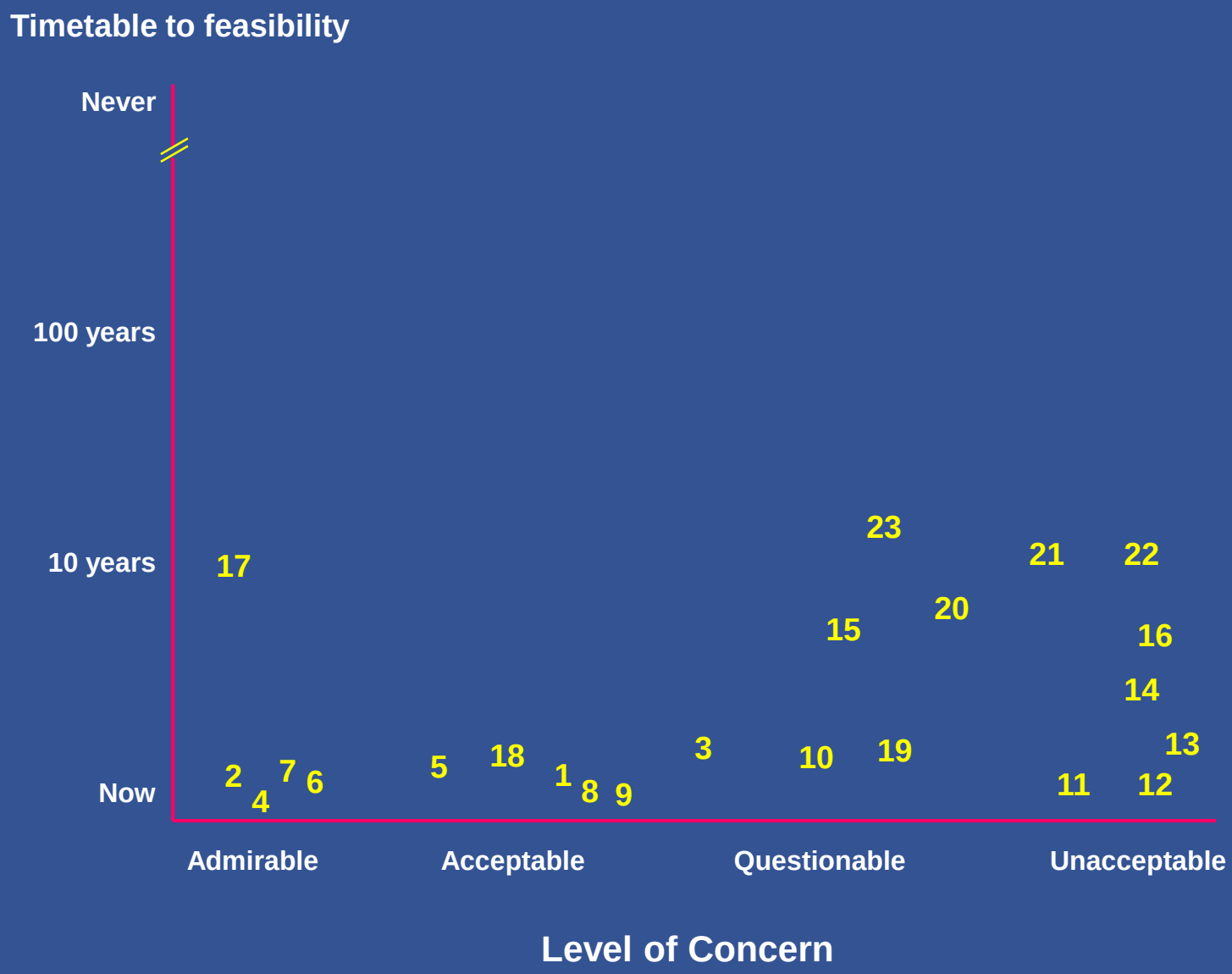
20. PGD for obesity



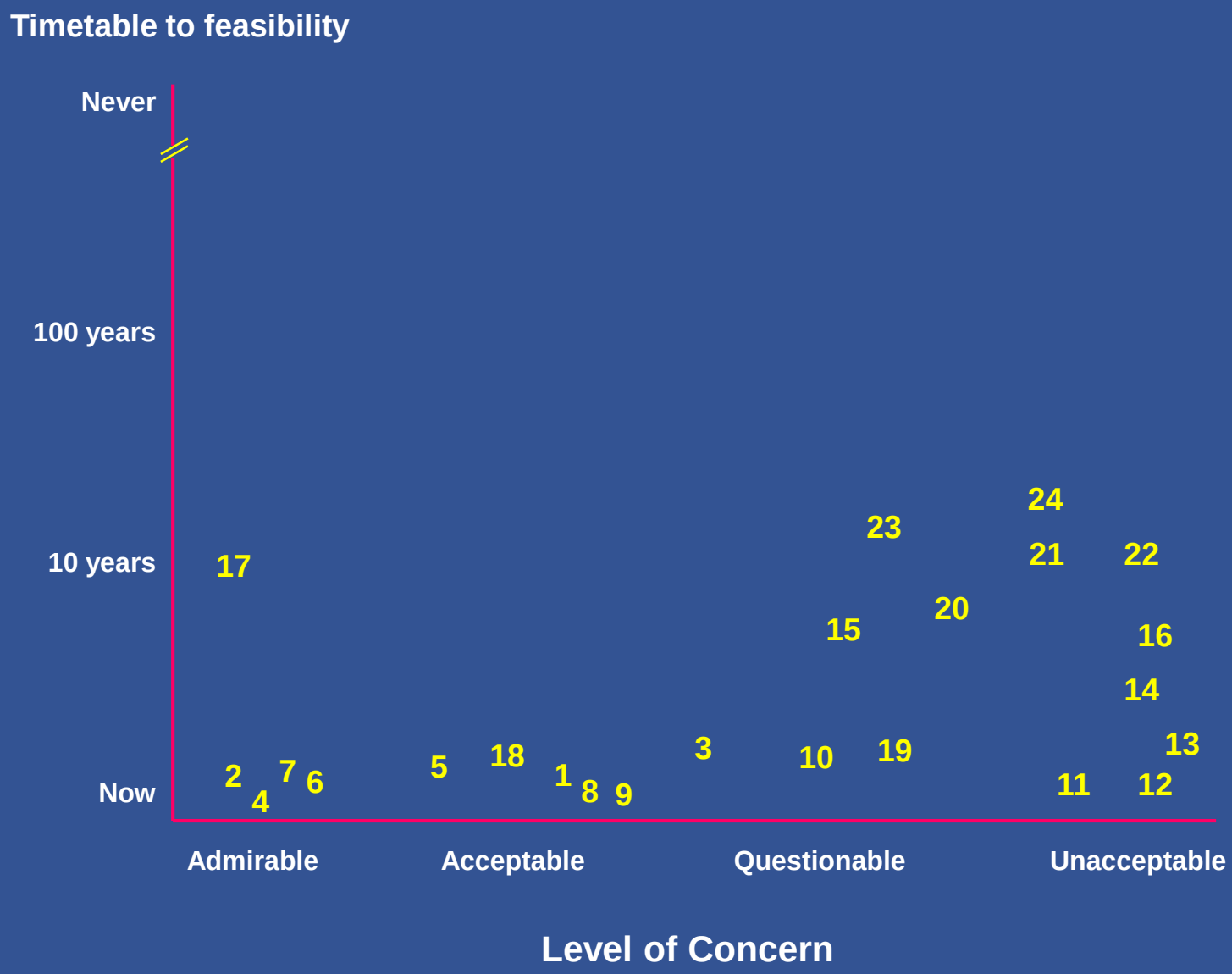
21. PGD for intelligence



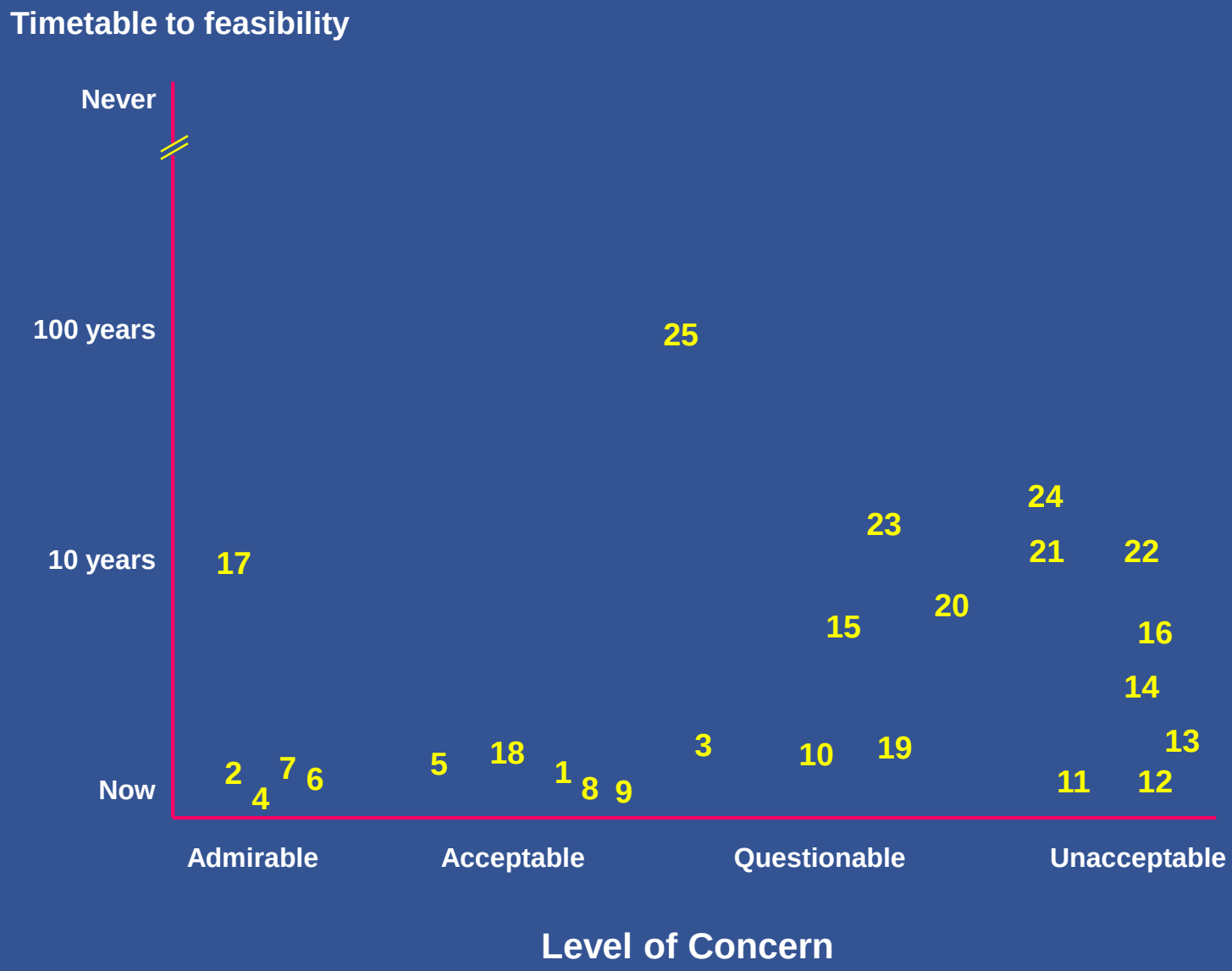
22. PGD for skin color



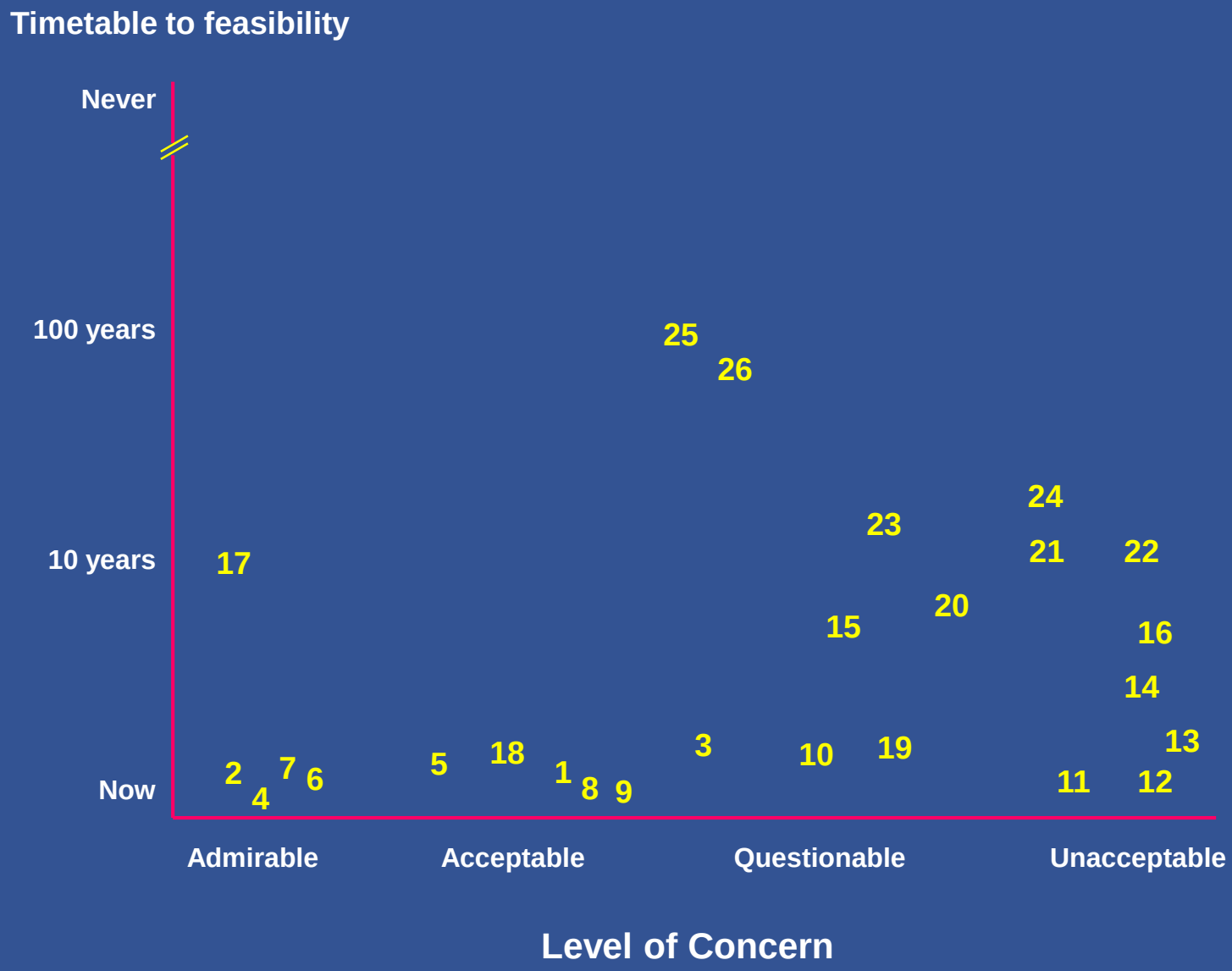
23. Drugs that keep normal people thin



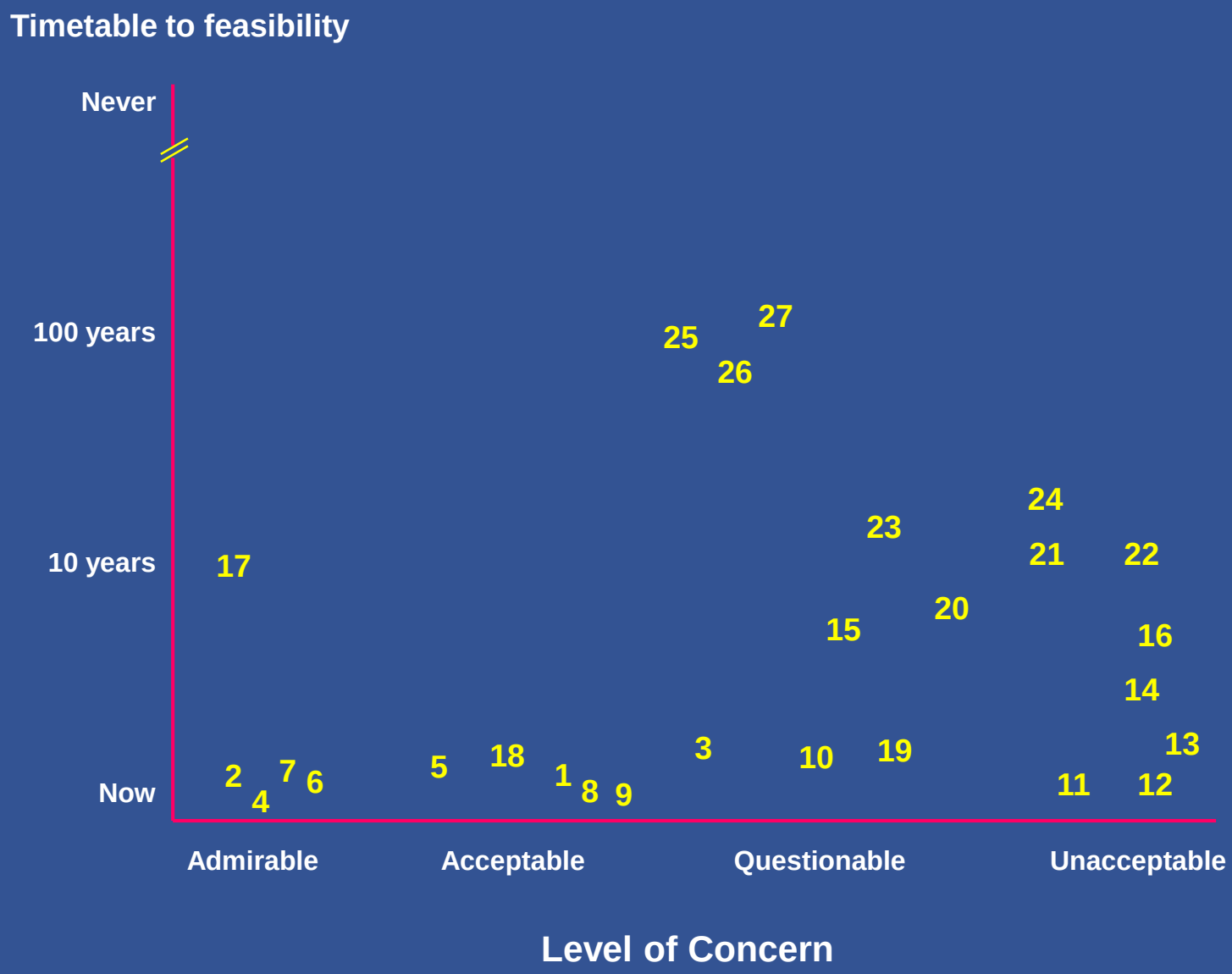
24. Human artificial chromosome transfer to embryos



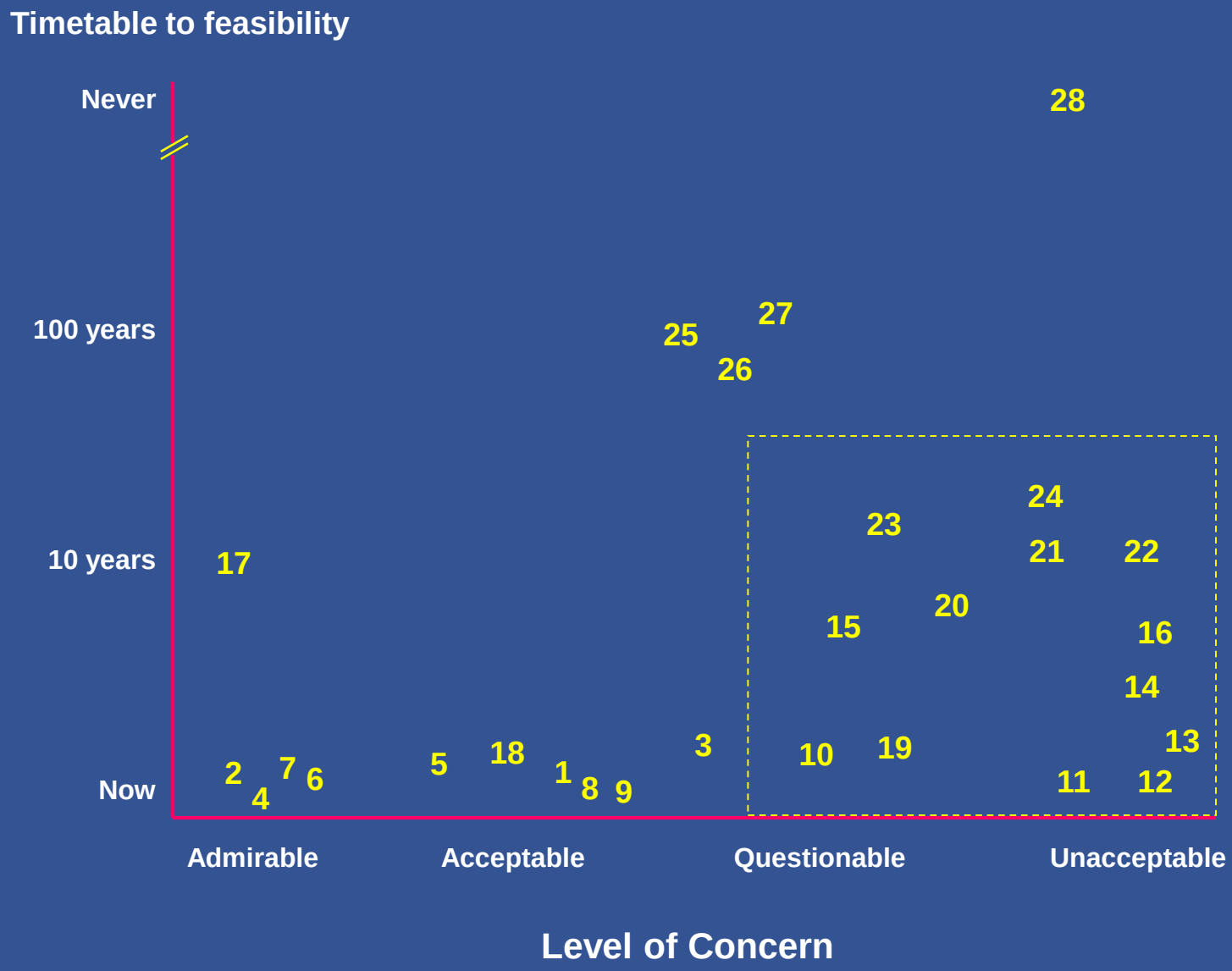
25. Never forget



26. Never sleep



27. Extension of life-span to 200 years



28. Designer babies with precisely predictable phenotype

Zone of Concern

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14. Sex selection
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21. PGD for intelligence
22. PGD for skin color
23. Drugs that keep normal people thin
24. Human artificial chromosome transfer to embryos