

# Linking physiological pathways to translational strategies

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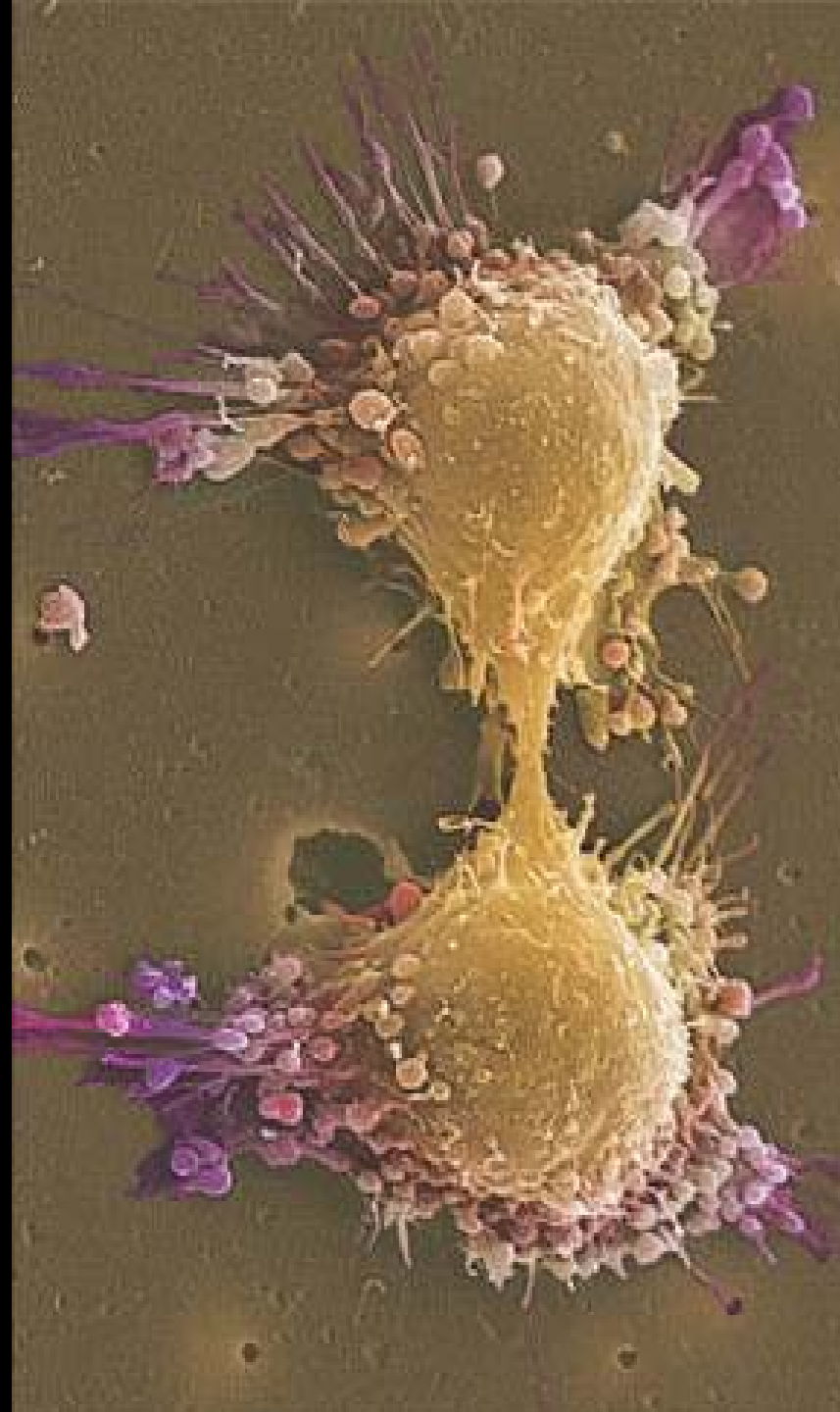
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University of California, Los Angeles

I have no commercial or other conflicts of interest to disclose



# Where we're at:

## 1. Mounting pre-clinical evidence

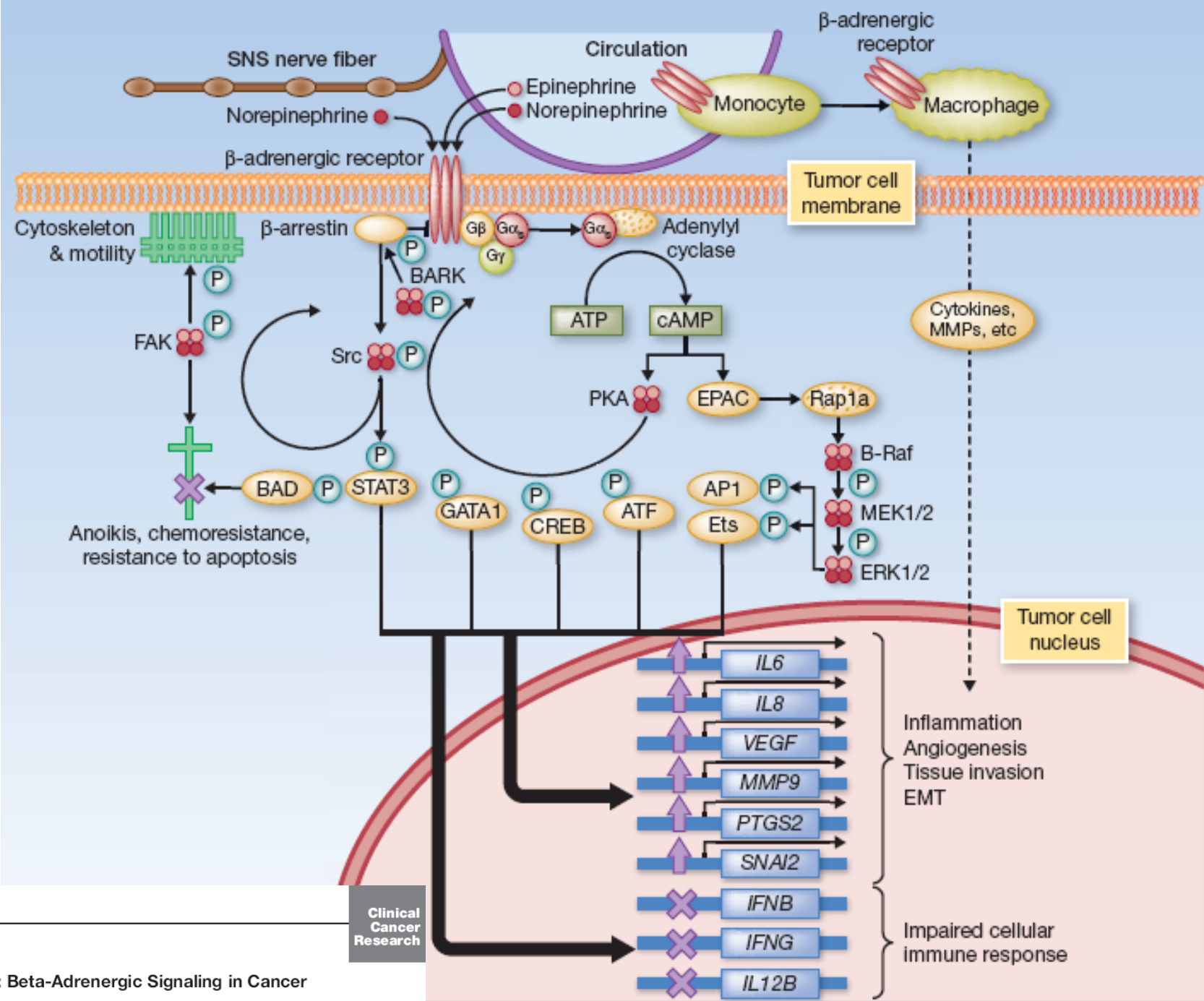
- Stress biology can causally impact tumor biology & cancer progression
- Most consistent effects: early progression/metastasis
  - Possible "initiation" exceptions: Inflammatory and viral-mediated initiation
- Neural-immune activation (macrophage) more prominent than neuro-immune suppression (cellular immune response)

## 2. Entrenched clinical/translational skepticism

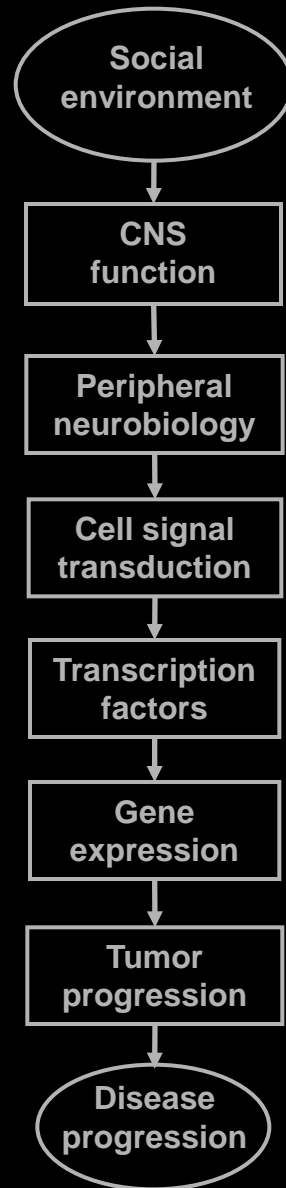
- Critics: we believe you - stress is bad for cancer.
  - Little credible evidence that stress-targeted interventions meaningfully impact clinical cancer progression.
  - (Also: Stress is everywhere, I can't measure it, blah blah blah)

## 3. Needed: a strong clinical success story

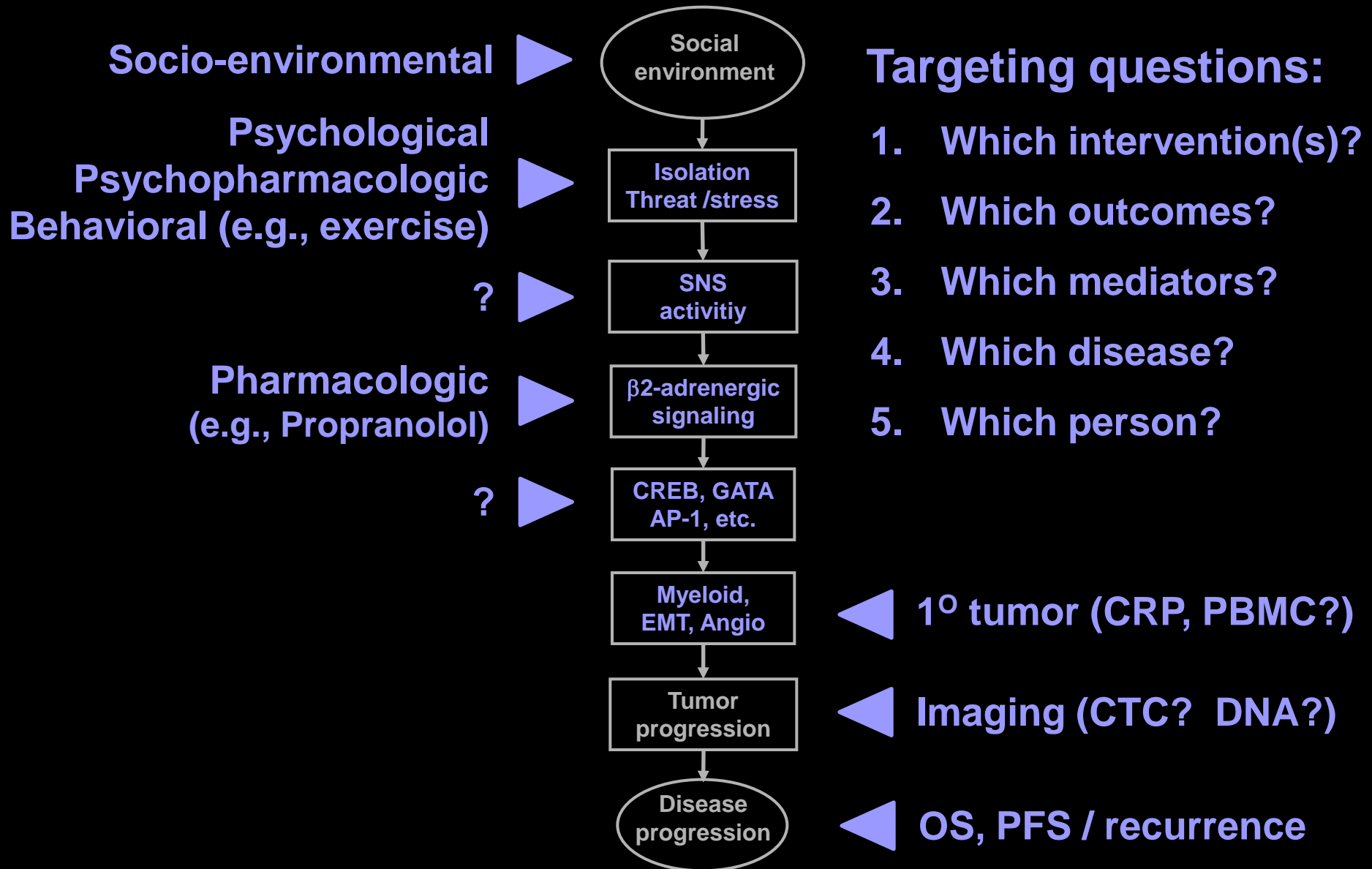
- Neural/endocrine-targeted intervention (e.g.,  $\beta$ -blockers)
- Social/behaviorally-targeted intervention (e.g., Andersen, Antoni)

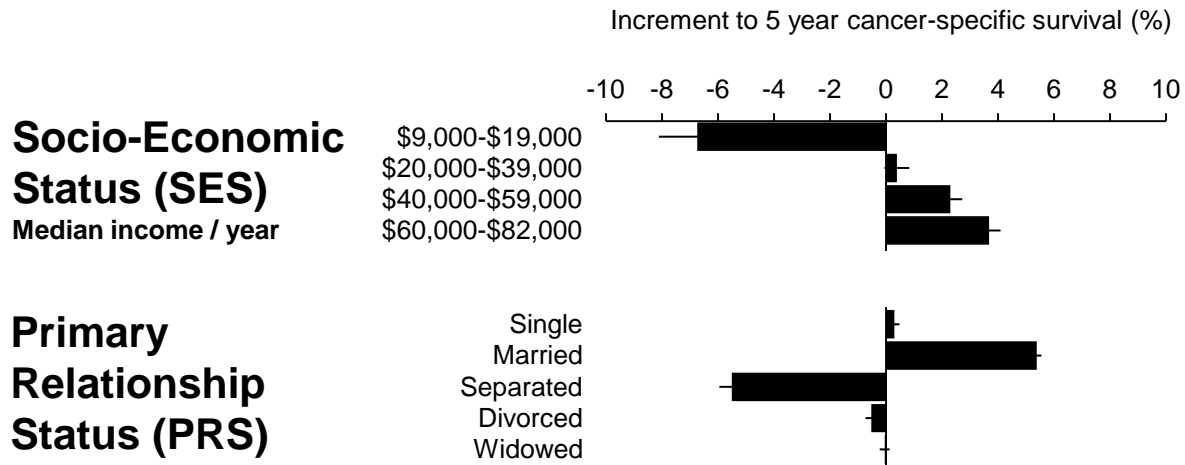


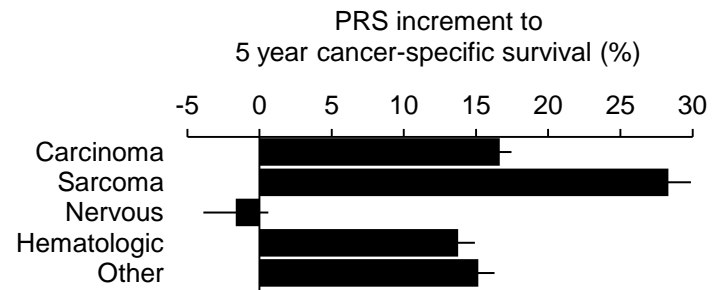
# Tumor “macroenvironment” model



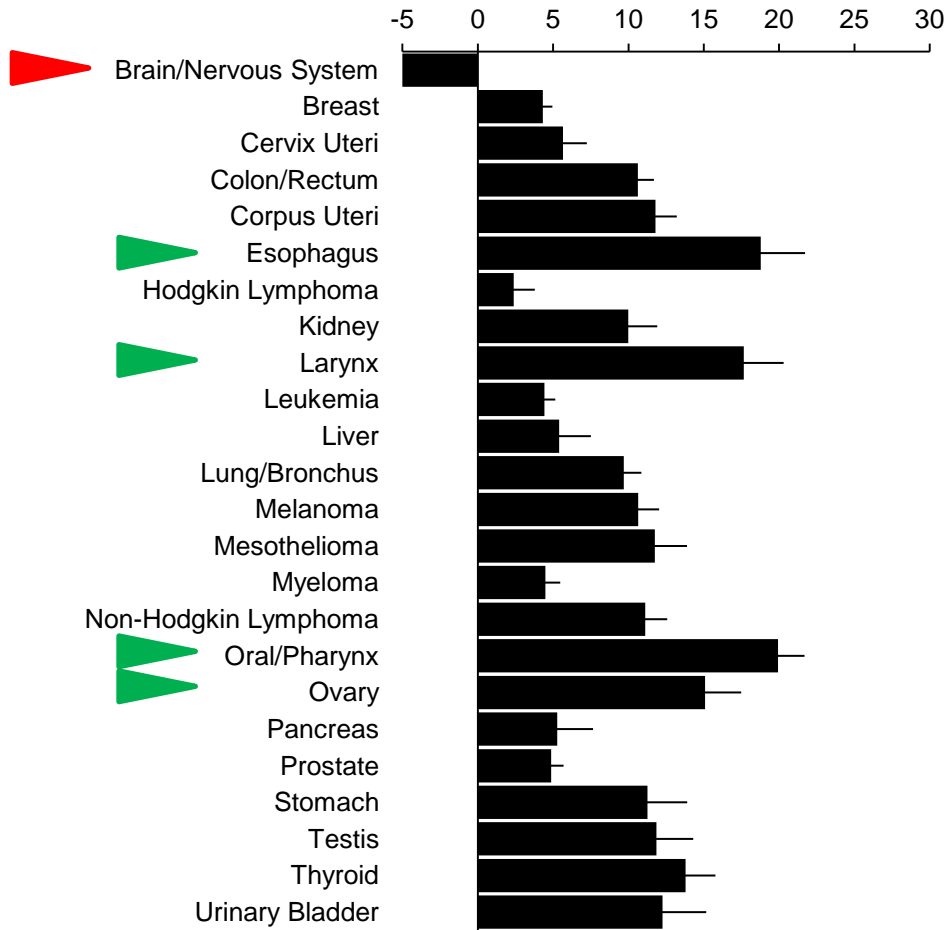
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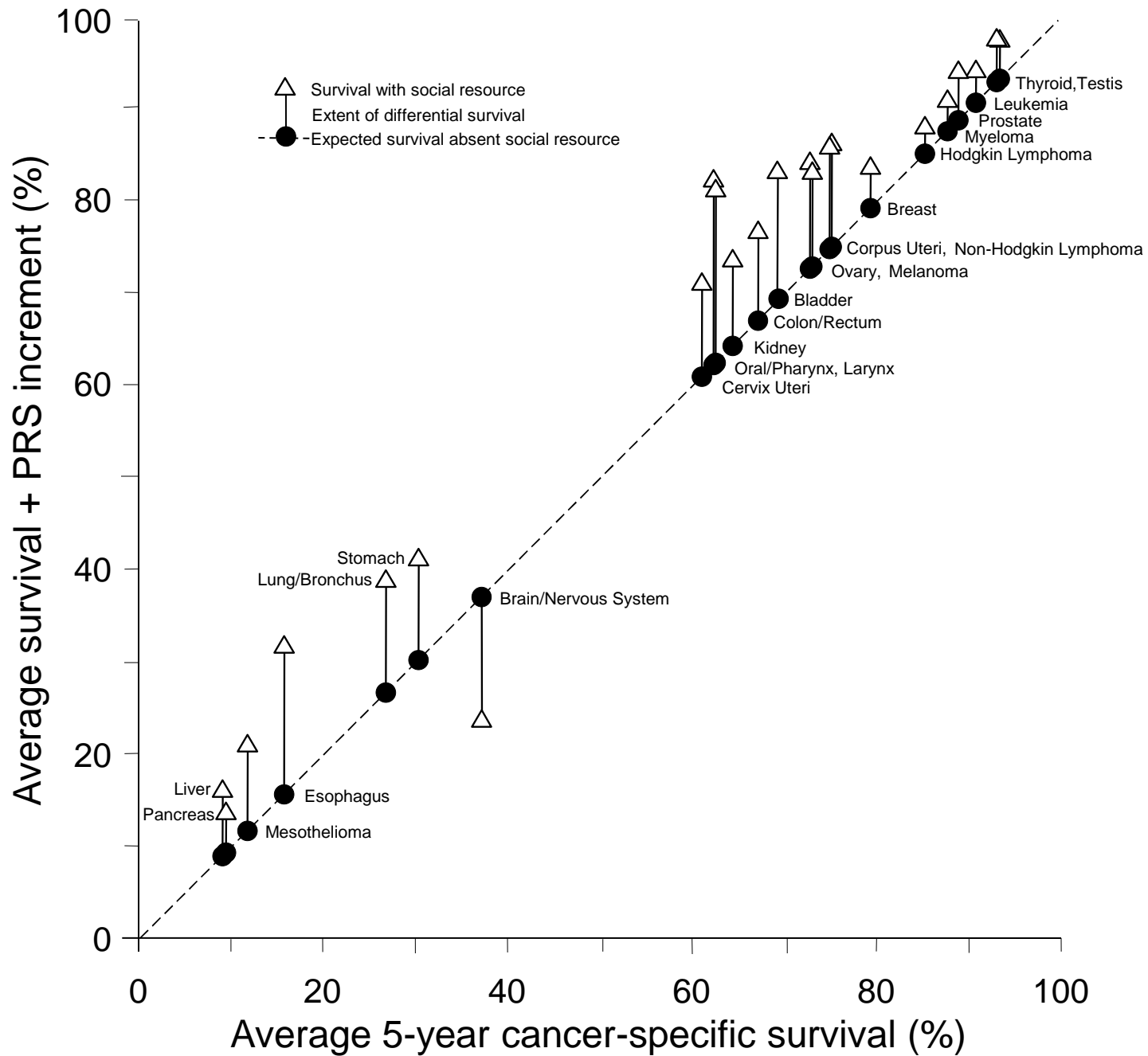




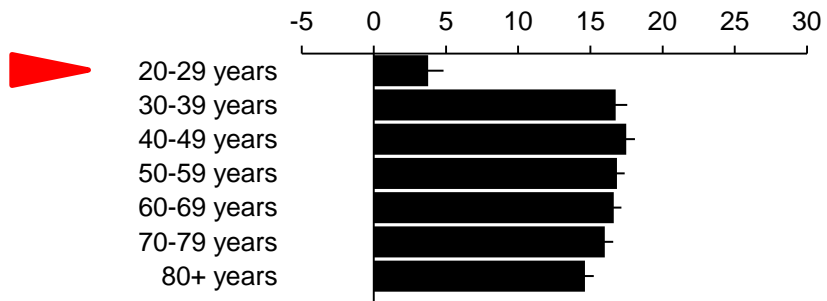
PRS increment to  
5 year cancer-specific survival (%)





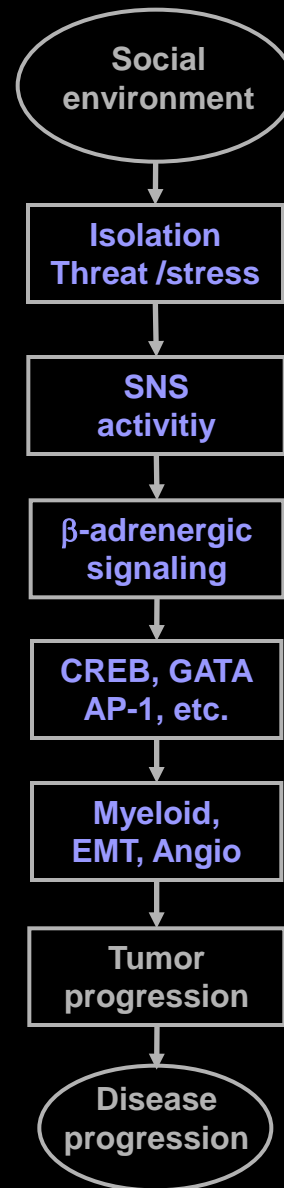


PRS increment to  
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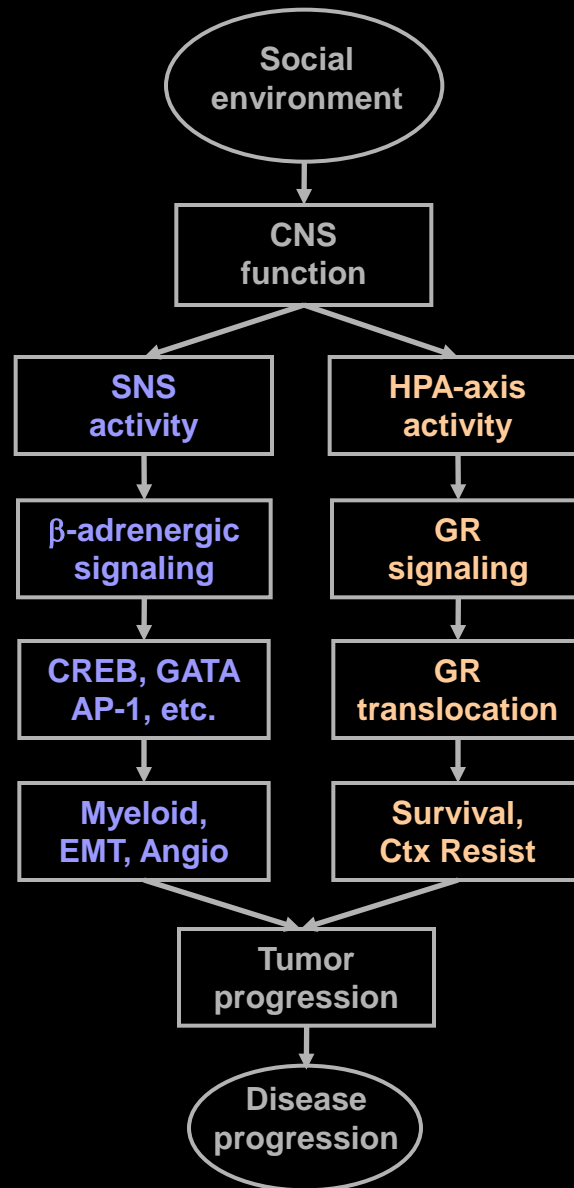
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## Targeting questions:

1. Which intervention(s)?
2. Which outcomes?
3. Which mediators?
4. Which disease?
5. Which person?

# Tumor “macroenvironment” model



# Translational horizon 2013:

## 1. Phase II biomarker data:

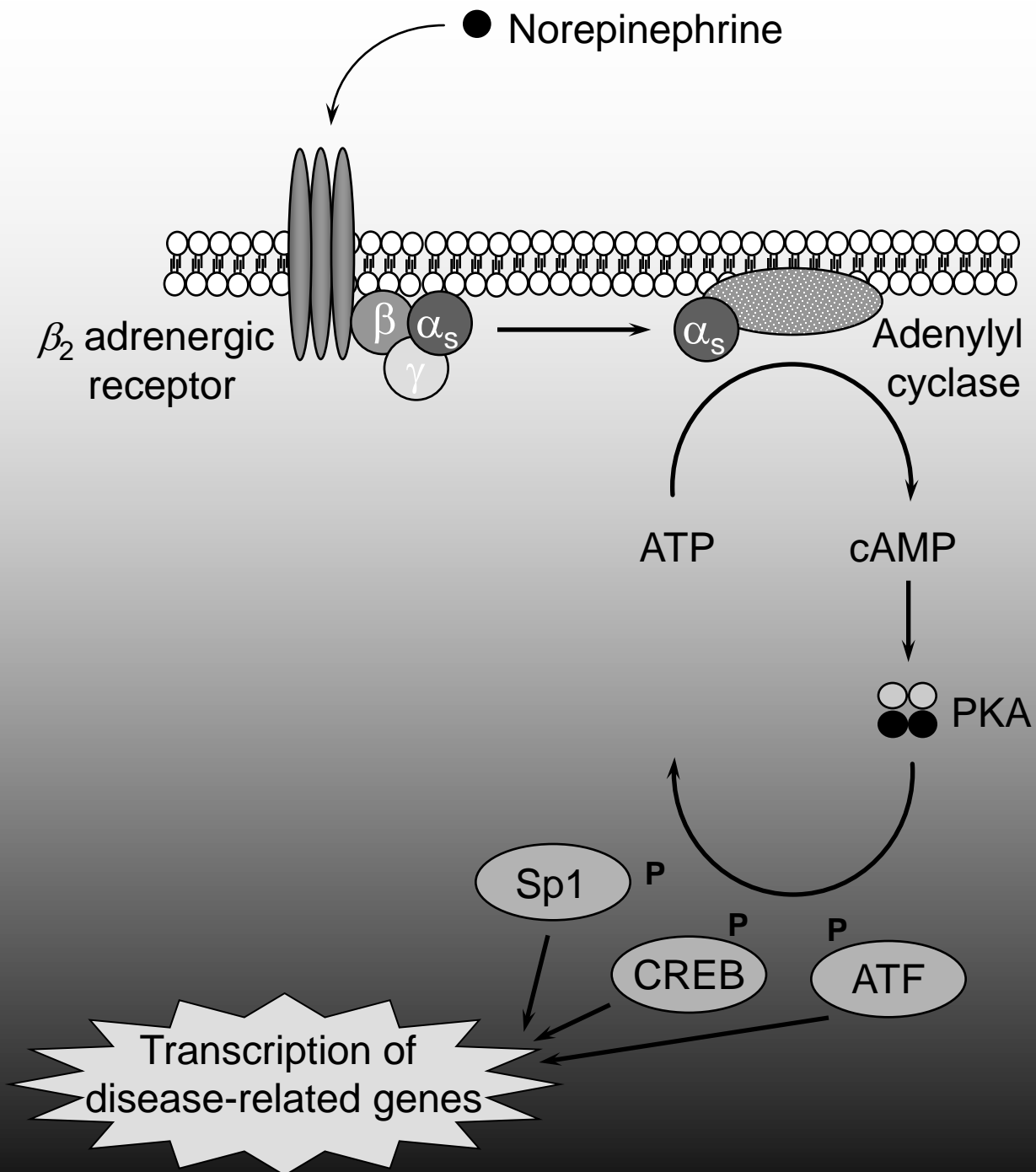
- “Small” randomized trials with biomarker outcomes
- Tumor biomarkers (imaging, window biopsy protein/gene, CTC)
- Gateway to well-powered clinical outcome studies

## 2. Externally “plausible” interventions

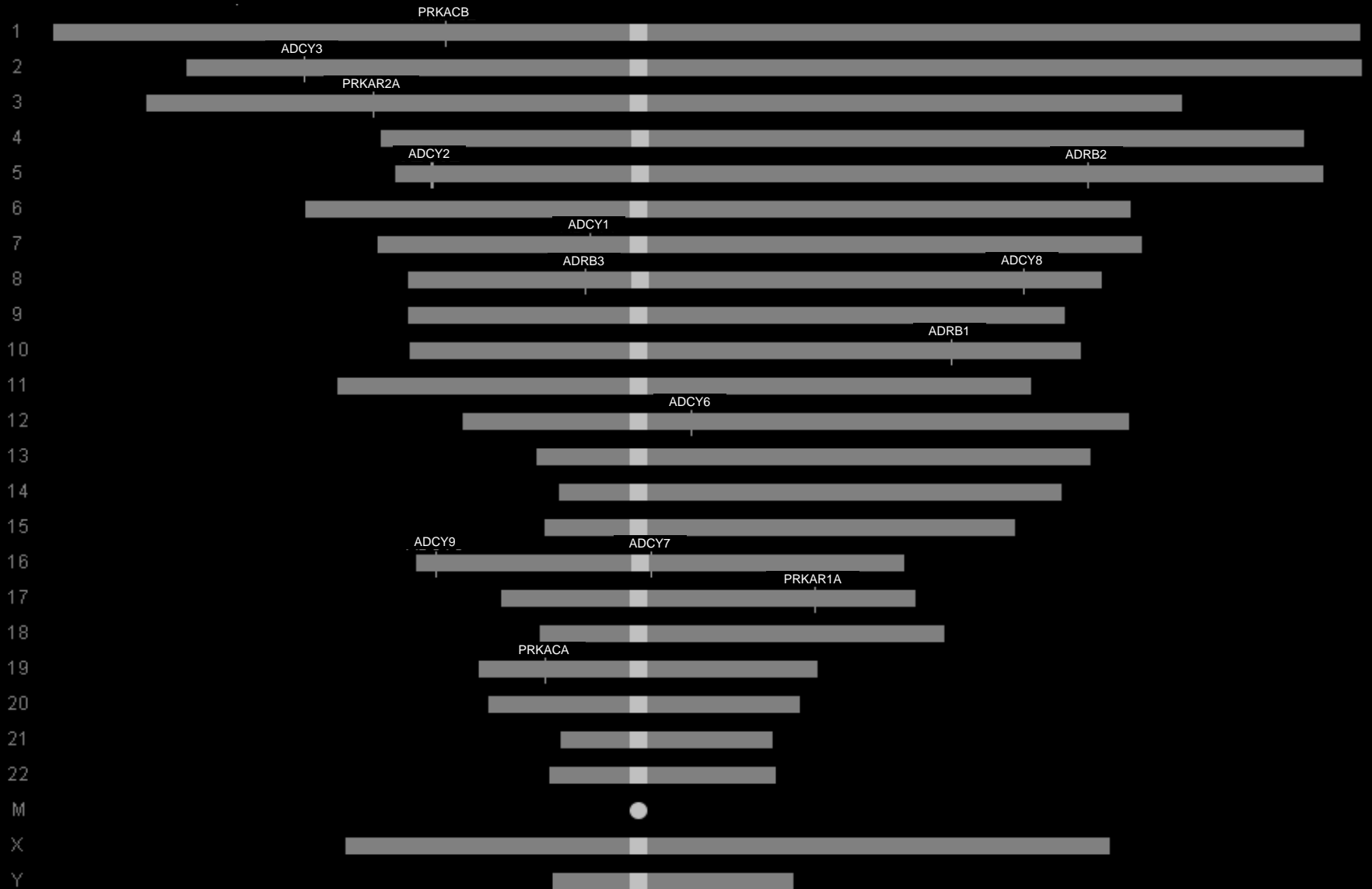
- Strong pharmacologic candidate: Propranolol
- Biomarker-validated behavioral interventions? (don’t forget physical activ)
- “Combination therapy” (e.g., Ben-Eliyahu)
- Be straightforward about feasibility / cost / scaling potential.

## 3. Personalization

- Stress targeting?
- Tumor genomic “sensitivity/resistance” to biobehavioral interventions

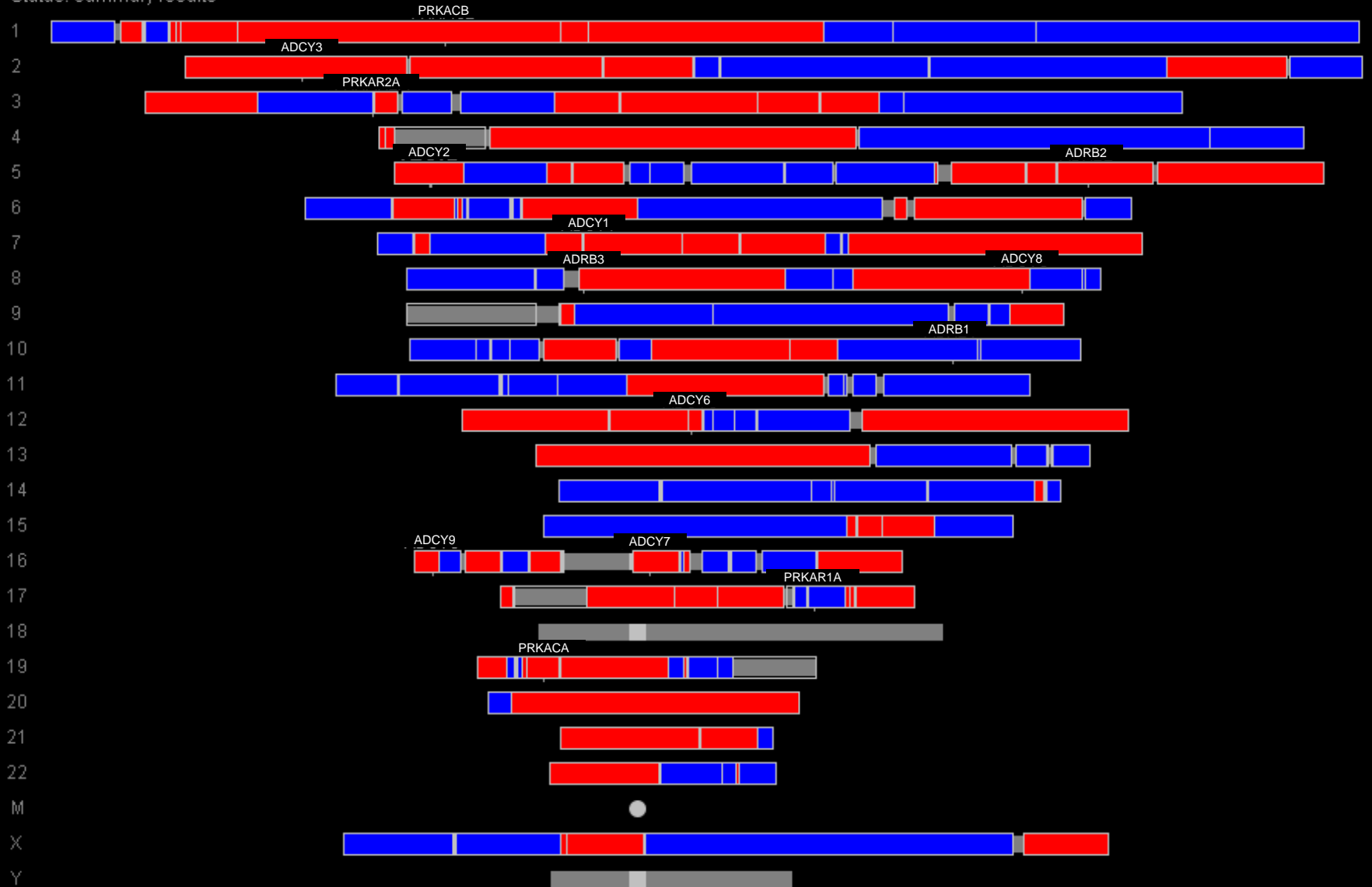


# Selection for $\beta$ -AR pathway gene alterations in ovarian cancer



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Status: summary results





# Selection for $\beta$ -AR pathway gene alterations in ovarian cancer

Gene	Functional relationship	Regional alteration	Consistency
<i>ADRB1</i>	+	-	-
<i>ADRB2</i>	+	+	+
<i>ADRB3</i>	+	+	+
<i>ADCY1</i>	+	+	+
<i>ADCY2</i>	+	+	+
<i>ADCY3</i>	+	+	+
<i>ADCY6</i>	+	+	+
<i>ADCY7</i>	+	+	+
<i>ADCY8</i>	+	+	+
<i>ADCY9</i>	+	+	+
<i>PRKACA</i>	+	+	+
<i>PRKACB</i>	+	+	+
<i>PRKAR1A</i>	-	-	+
<i>PRKAR2A</i>	-	-	+

◀ 13 / 14:  $p = .00006$

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