Provoca'v e Ques' ons

I. What we've learned
II. What might be next

Part I: What have we learned?

Based on:

1. Review of PQ Process (Workshops, Web, PQ Exec Comm, PQ Program Team, Review)

2. Evalua I on of PQ applica I ons, funded grants, and PIs grant histories

3. Individual or group interviews with 200+ NCI staff from all Divisions/Centers who were engaged with review and funding of PQ grants

PQs by the Numbers

RFA	Number of Ques'ons	New: Reused: Rewri@e n	Categories					
2011	24	24:0:0	None	1	754	56	7.4	21.5
2012	24	10:5:9	Risk And PrevenIon Tumor Development Detect, Diag, & Prog Therapy and Outcomes	2	777	93	12.0	39.2
2013	20	10:4:6	Risk And PrevenIon Tumor Development Detect, Diag, & Prog Therapy Clinical EffecIveness	2	?	?	?	?

What is special about PQs?

- Ask research quesI ons in unexplored areas
- Pose quesI ons rather than idenI fying projects
- Rely on community for quesI on development
- Go from quesI on to RFA in 3 or 4 months
- SI mulate a true trans-NCI process

There has been considerable interest in PQs

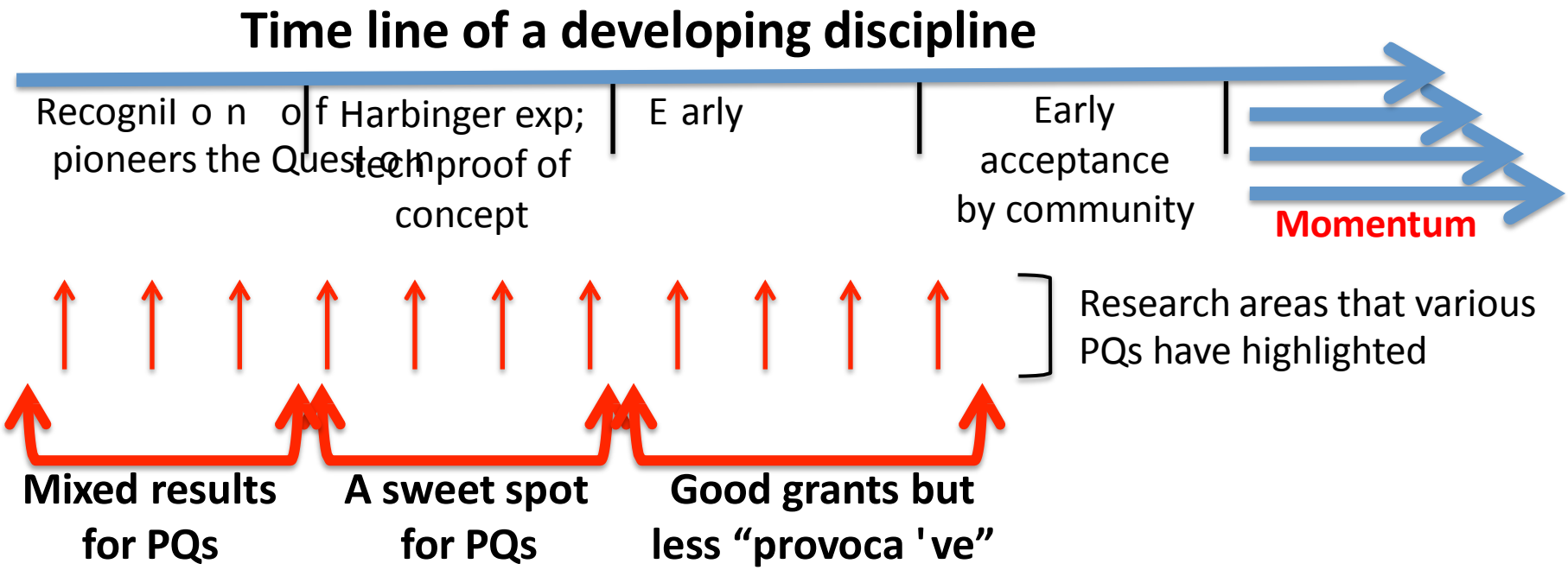
- PQ Workshops are producI ve with challenging discussions
- Research community remains commia ed to a a end and parI cipate
- NCI staff is enthusiasI c; some individuals highly supporI ve
- Good press in research journals
- Other NIH InsI t u tes are curious with some adopI on of related processes
- PQs have been used to teach courses and to organize conference sessions
- PQs now have gone interna I onal; first co-organized sessions with India will occur in Oct/Nov 2014 with parI cipants from across the globe

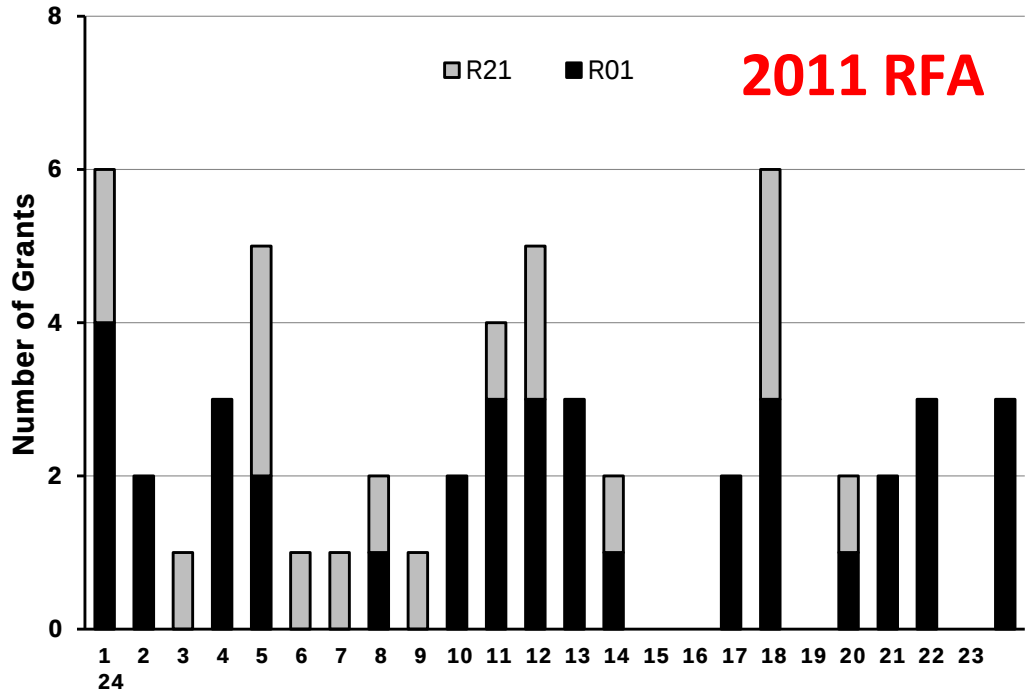
Where have the problems been?

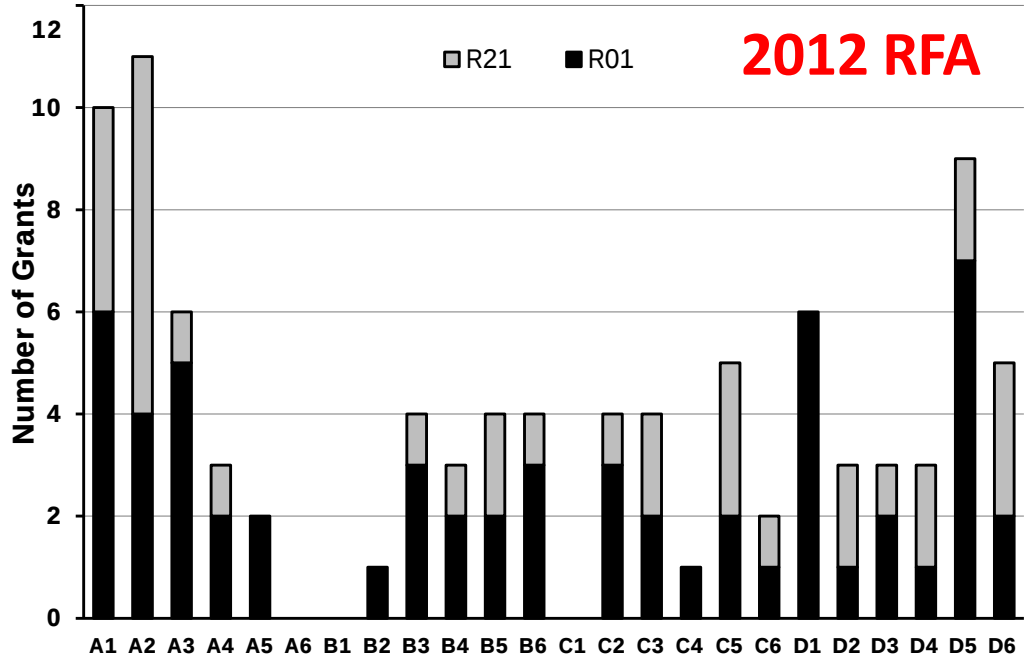
- Bringing PQs to the community's attention
- Dealing with the logistics of 750+ applications, including Program and Review processes
- Making sure the applications attempt to answer the questions
- Getting NCI Program Staff more involved in PQ development

Are we making progress?

- Too early to give a well informed answer
  - Under 2 years for the earliest funded grants
- But clear that some PQs hit a ready audience, some helped build a field, and some PQs fell into space







Funding by PQ

2011

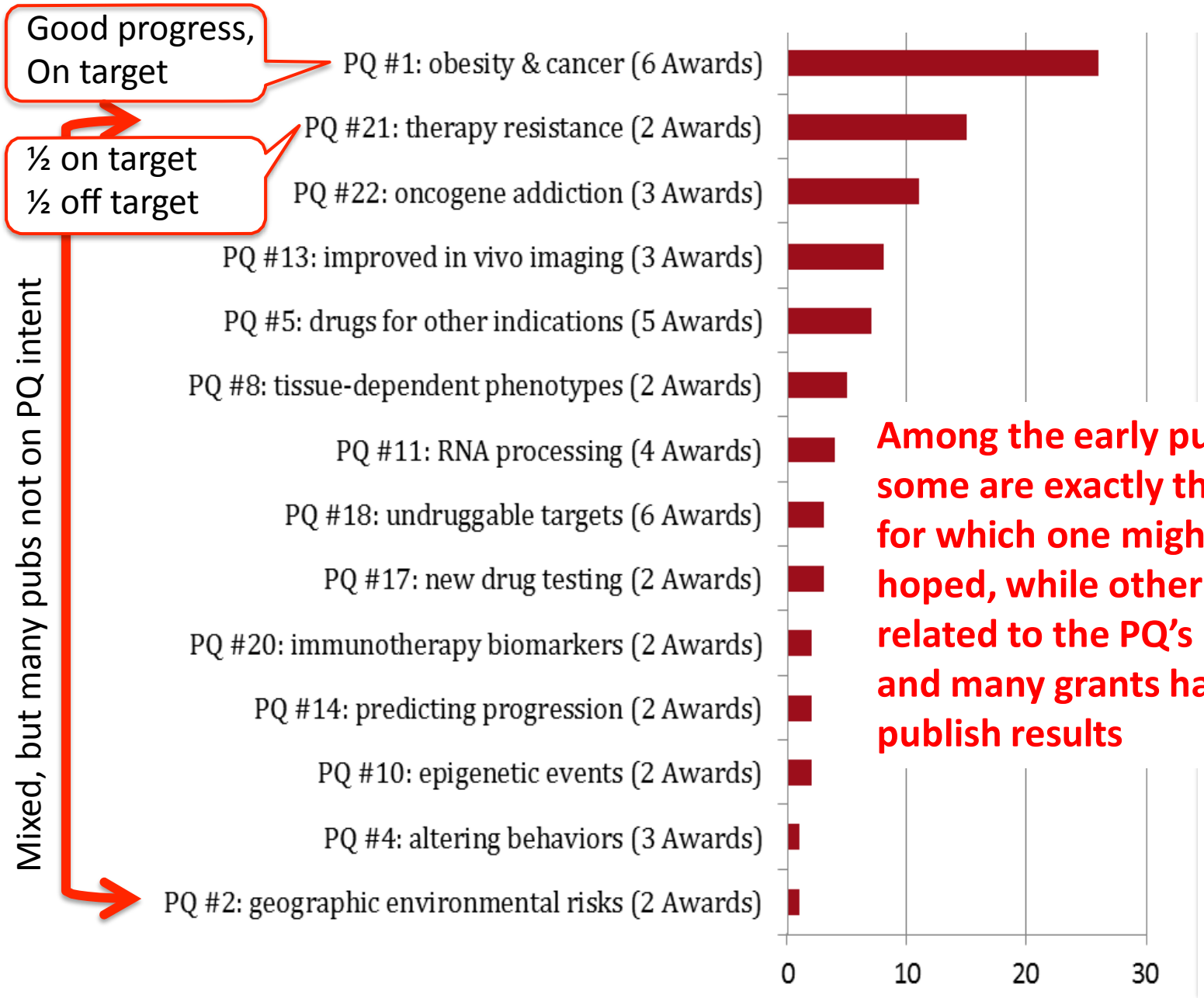
- No awards made for 4 PQs
- Highest number of awards were made to PQ1 (Obesity in CA) and PQ18 (undruggable targets)
- Highest success rate was for PQ4 (altering behaviors)

2012

- No awards made for 3 PQs
- Highest number of awards were made to PQA2 (Obesity in CA)
- Highest success rates were for PQA4 (measuring risk) and PQC5 (improved in vivo imaging)

Ratio of R01 to R21 varies by PQ

PUBLICATIONS THAT CITE SUPPORT FROM FIRST RFA



Among the early publica' ons, some are exactly the first steps for which one might have hoped, while others aren't related to the PQ's intent at all and many grants have yet to publish results

Transformed Drosophila cells evade diet-mediated insulin resistance through wingless signaling.

Sin3a acts through a mull-gene module to regulate invasion in Drosophila and human tumors.

Adipose I s s u e invariant NKT cells protect against diet-induced obesity and metabolic disorder through regulatory cytokine producI o n .

C u g n g edge: CD1d restricI o n a n d T h 1/Th2/Th17 cytokine secreI n by human Vd3 T cells.

Human invariant NKT cell subsets differenI a l l y promote differenI I o n, and b o d y producI o n , and T cell s mula I o n by B cells in vitro. Ex vivo analysis of resident hepa I c pro-inflammatory CD1d-reac v T cells and hepatocyte surface CD1d expression in hepa I I s C .

CD1d favors MHC neighborhood, GM1 ganglioside proximity and low detergent sensiI ve membrane regions on the surface of B lymphocytes.

Obesity promotes breast cancer by CCL2-mediated macrophage recruitment and angiogenesis.

Ether lipid genera I n g enzyme AGPS alters the balance of structural and signaling lipids to fuel cancer pathogenicity.

Cancer cells incorporate and remodel exogenous palmitate into structural and oncogenic signaling lipids.

Systems-based discovery advances drug development.

Molecular staging of node-negaI ve pa I ent with colorectal cancer.

Obesity pharmacotherapy: what is now?

Informa I o n h i erarchies opI mize pa I ent-centered soluI o n s .

Transla I o n a l medicine individualizes healthcare discovery, development and delivery. Foreword.

GUCY2C: at the intersecI o n o f o b esity and cancer.

ImmunotherapeuI c strategies to target prognosI c cancer predicI ve markers of cancer.

New advances in models and strategies for developing anI -obesity drugs.

Advances in cancer immunotherapy.

Colorectal cancer immunotherapy.

Transla I n g colorectal cancer prevenI on t h rough the guanylyl cyclase C signaling axis.

IntesI n a l GUCY2C prevents T cell-mediated oncogenic gene desmoplasia and hyperproliferaI on in colorectal cancer.

Anti-obesity pharmacotherapy: new drugs and emerging targets.

Managing the innova I on supply chain to maximize personalized medicine.

Guanylyl cyclase C as a biomarker in colorectal cancer.

Energy balance, polymorphisms in the mTOR pathway, and renal cell carcinoma risk.

Transformed Drosophila cells evade diet-mediated insulin resistance through wingless sign

Sin3a acts through a mull-gene module to regulate invasion in Drosophila and human tumors.

Flies and insulin signaling

Adipose I s s u e invariant NKT cells protect against diet-induced obesity and metabolic disorder through regulatory cytokine producI o n .

Cug n g edge: CD1d restricI o n a n d T h 1/Th2/Th17 cytokine secreI o n b y human

Humans and immune response

Obesity PQ

InteresI ng results, but very different

how obesity might increase CA risk

Tepatocyte surface CD1d expression in hepaIT s

CD1

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angiogen

Mice and immune response

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Humans and lipid signaling

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Humans and cGMP signaling

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cancer.

Managing the innova I on supply chain to maximize personalized medicine.

Guanylyl cyclase C as a biomarker in colorectal cancer.

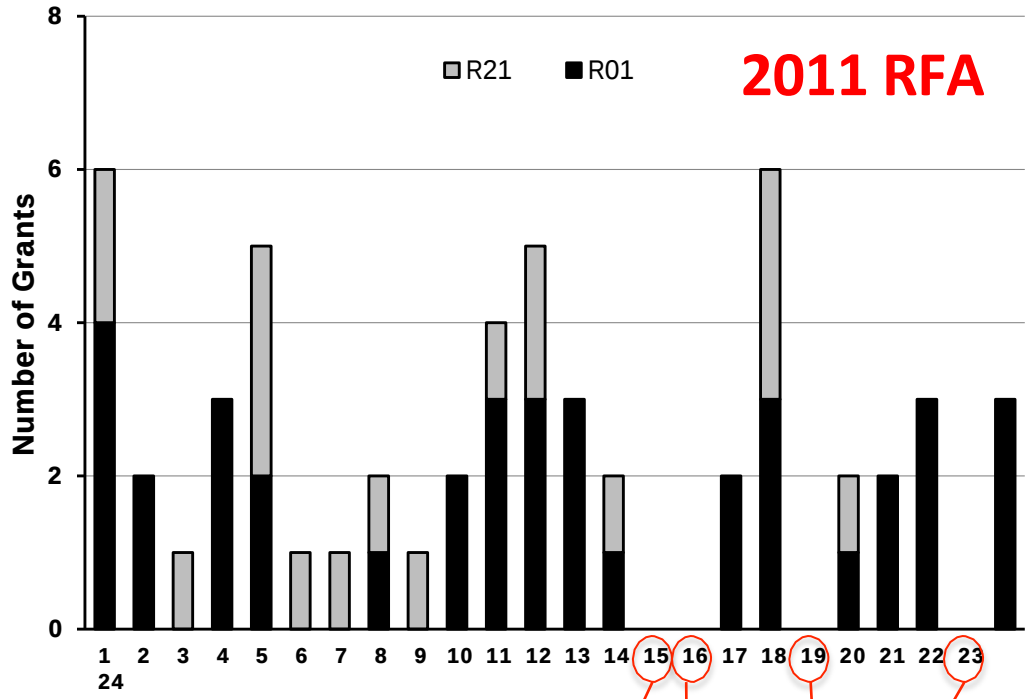
Energy balance, polymorphisms in the mTOR pathway, and renal cell carcinoma risk.

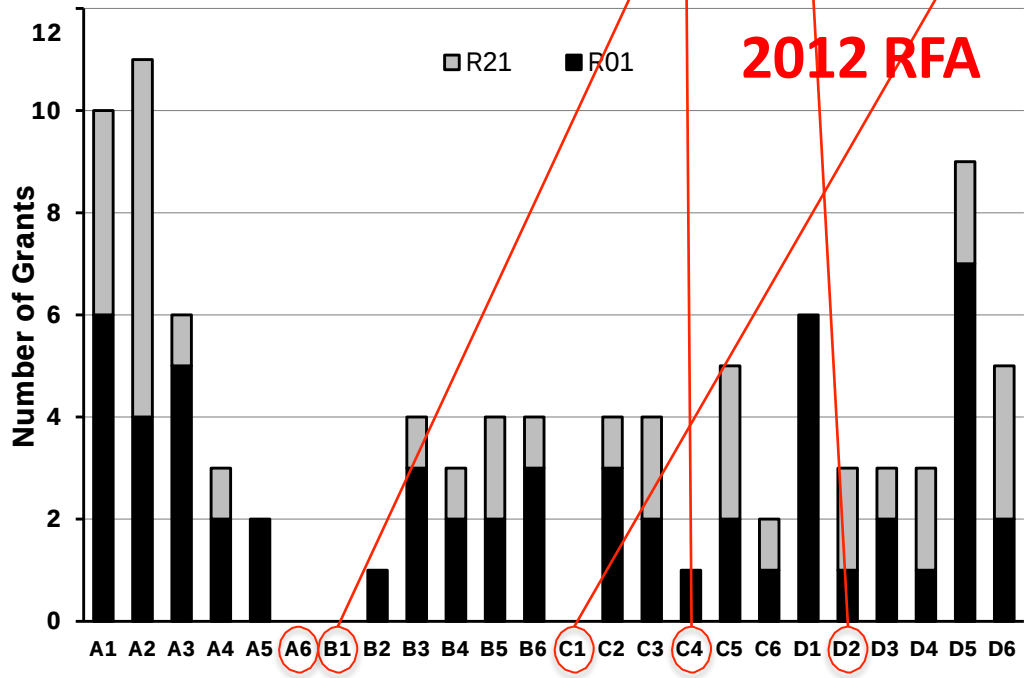
Humans and energy balance

PQ. How does obesity contribute to cancer risk?

- 6 funded applica I ons in first PQ RFA
- All groups are making progress, some with impressive output
- Groups don't propose same mechanisms, and progress is spread among the approaches
- Now there are 11 more funded applica I ons from 2012 RFA
- PQ reI red before 2013 RFA because now good scienI fic momentum

NCI should play role in staging interacI ons to sI mulate progress





Why do some Ques' ons fail?

15. Why second cancers at higher rate?
16. Sig of tumor cells at second site?
19. Why does chemotherapy work?
23. Why some tumors become malignant?

A6. Risk factor suscepI b i l i ty during development

Poten' a l reasons

- The field isn't ready to consider.
- We are missing key reagents/resources.
- The right people aren't applying.
- The quesIon is poorly wriaen.
- Others?

Some Observa'ons from Program Evalua'on

- Sta Isl cally significance increase (5.2%) in publica I ons associated with PQ quesI on areas following issuance of RFA
- Sta Isl cally significant increase (6.5%) in the propor I on of relevant grant applica I ons (excluding PQ applica I ons); varied by quesI on area.
- 1/3 of PQ grant applica I o n s f a i l ed to meet a simple measure of scienI fi c relevance to the quesI o n s u b j ect descrip I o n
- Roughly 1/2 of applica I o n s s u b mia ed to 2011 and 2012 RFAs were judged to be novel
- 1/3 of applica I o n s s u b mia ed to 2011 and 2012 RFAs showed strong similarity to a given inves I gator's prior NIH grants
- PQ RFAs do as well or bea er than other high profile NIH FOAs (New Innovator, Transforma I ve, Eureka, Pioneer, High-Impact, IMAT, 2010 NCI RFAs) at a a rac I ng new inves I gators and inducing them to submit other NCI applica I ons

What have we learned?

1. PQ InitI a I ve asked both the community and NCI to change some standard procedures. NCI has adapted and appears ready to take next steps. The community adopI on has been mixed.
2. The PIs who are applying are already in the selected PQ research discipline or are looking for new funding opportuniI es.
3. Many invesI gators sI l l d o n ot know about PQs.
4. Although it is sI ll early, it seems reasonable to suggest that simply asking quesI ons, even excellent ones, doesn't necessarily lead to research progress in the PQ area. If we want this, we'll need to be more acI ve both in a a racI ng bea er applica I ons and providing long term help sI mula I ng the field.

Part II: What's next for PQs?

SuggesI ons based on:

1. Review of applica I ons and funded grants in first 2 years of PQ RFAs
2. Individual or group interviews with 200+ staff from all Divisions/Centers who were engaged with review and funding of PQ grants

Provoca' ve Ques' on Renewal

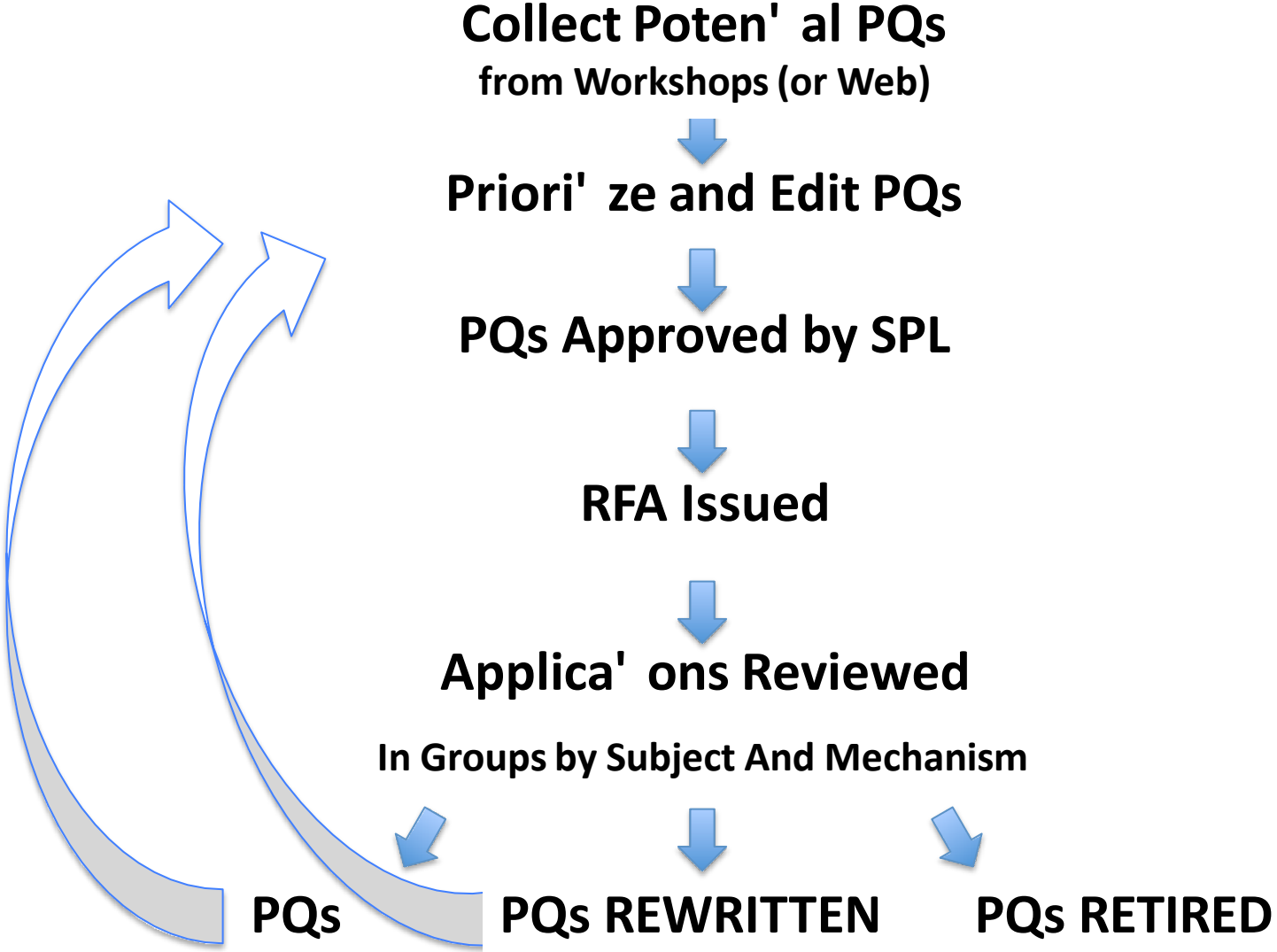
Request:

- Renewal of the PQ RFA
- Seeking approval for 3 RFA issuances (same number as first approval)
  - 2 year acI ve period for each RFA issuance
  - Set aside @ $20M/yr (less than 2011 ($22M) or 2012 ($39.2M)
- Alter RFA language to allow withdrawal of applica I o n s t h at are not scienI fi cally responsive to PQ's intent
- Allow R01s for 5 yrs, rather than current 4 yrs
- Allow A1 resubmissions (not allowed at present)
- CompeI I ve renewals move to RPG pool (as done currently)
- Allow mechanism (R01, R21, U01) to be determined by content of specific PQ (approved by Director with advice from SPL members)
- 3 sets of metrics to measure success, discussed in detail below

Other changes are planned, outlined below

CURRENT PQ PROCESS

for each new issuance of RFA



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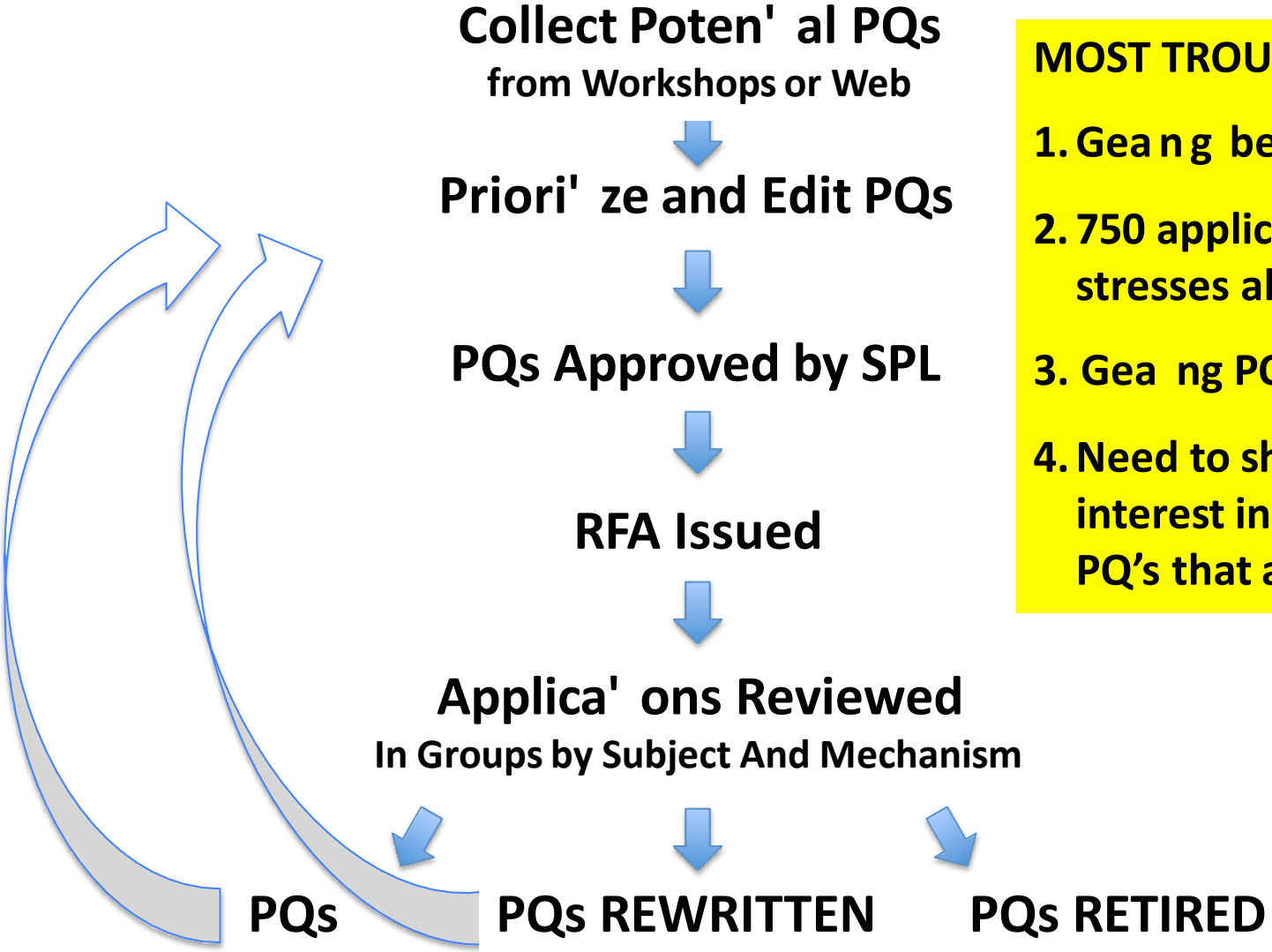


MOST TROUBLING ISSUES:

1. Gea n g best applica ' ons?
2. 750 applica ' ons/yr stresses all parts of system
3. Gea ng PQs answered?
4. Need to show co n ' nued interest in subject areas of PQ's that are re' red?

NEXT STEPS IN PQ PROCESS

SUGGESTED CHANGES — I:

1. Develop the RFA for each PQ based on its content
   - Mechanism — R01 and/or R21, or U01; emphasize mulI p l e PIs
   - Other customizaIo n s for the specific PQ
2. Develop more acI ve noI fi caI o n of PQ release
   - Target likely applicants to inform about specific PQs
   - Develop Smartphone app (Perhaps for all NCI RFAs, PARs, PAs??)
3. Reduce number of PQs to 8 – 12 per RFA cycle:
   - Diminishes pressure on divisions and review
   - Raises aaenI o n o n t h e presented quesI o n s
4. Extend RFA acI ve period to 2 years
   - Rapid turnover of quesI o n s / a p p l i caIo n s i s n't necessary
   - Rapid fire submission dates may hurt development of carefully considered applicaIo n s
5. Add addiI o n a l I me to quesI o n b u i l d i n g cycle to allow each division to review and comment on potenI a l q u esI o n s p rior to SPL decision
6. Add language to RFA to demand applicaIo n s a d d ress the intent of PQ

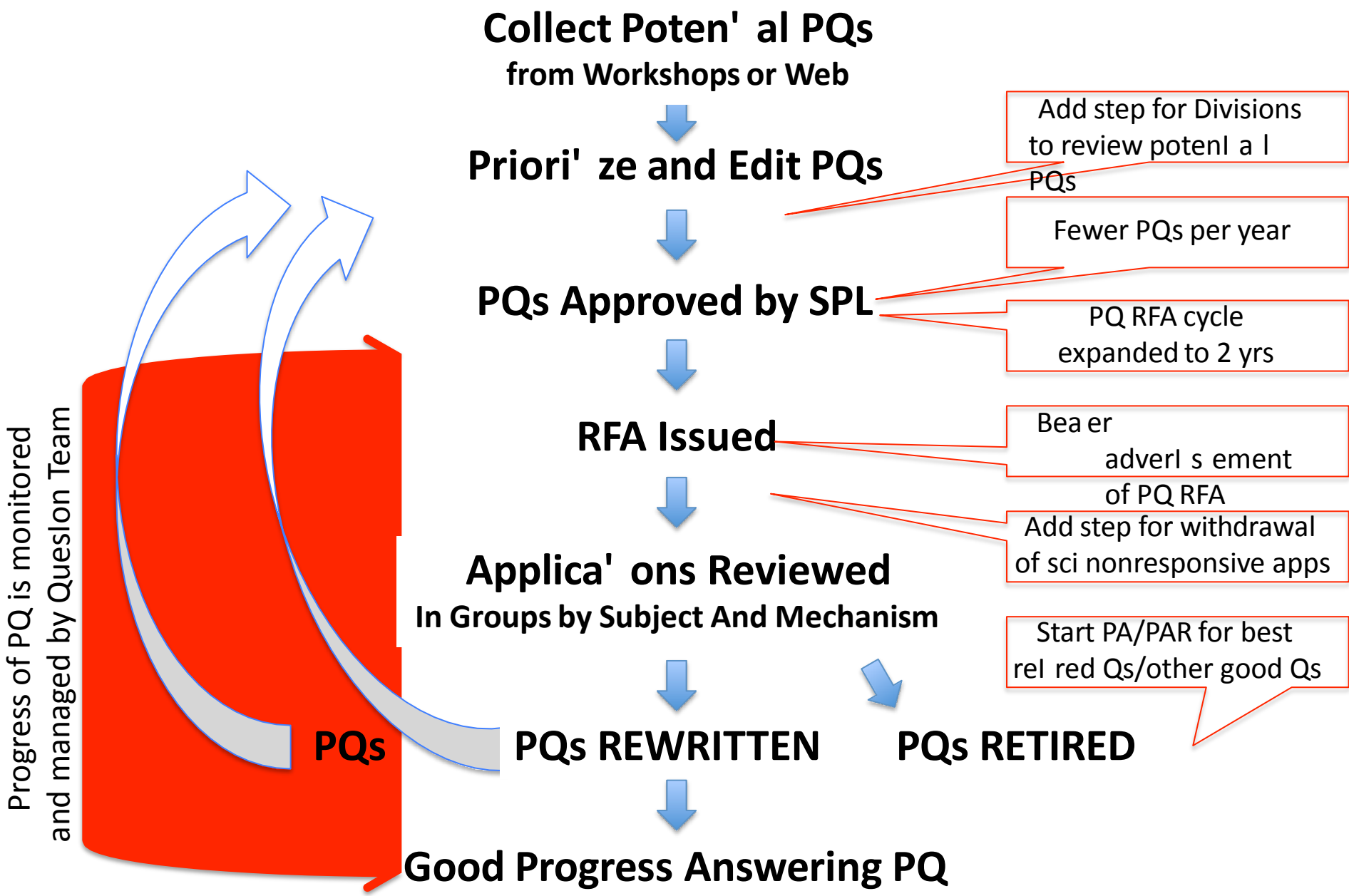
NEXT STEPS IN PQ PROCESS

SUGGESTED CHANGES — II:

7. Add additional time in review cycle to allow withdrawal of scientifically nonresponsive applications prior to review
8. Establish a small cross-division team to manage each PQ: Teams coordinated by OD, but team becomes the "owner" of PQ and its *answer*
   - Determines customization for each PQ
   - Responds to inquiries from potential applicants
   - After submissions, determines which submitted applications are nonresponsive to PQ's intent
   - Follows progress of science to answer question
   - Recommends if question stays active, needs re-writing, or is retired
   - Manages success of question
     Should we sponsor meetings? Encourage PI interactions? Are new resources needed to move science forward?
   - If the PQ does not attract good applications, determine why not. Just bad question or does the field need something to allow success?

7. Issue Question PA/PAR to highlight select questions that are retired

SUGGESTED PQ PROCESS



Du' es of “Ques' on Team”

PotenI a l PQs sent to Divisions to judge enthusiasm and to determine if Division has interest in PQ

All Divisions interested in PQ nominate members to form PQ Team

PQ CYCLE

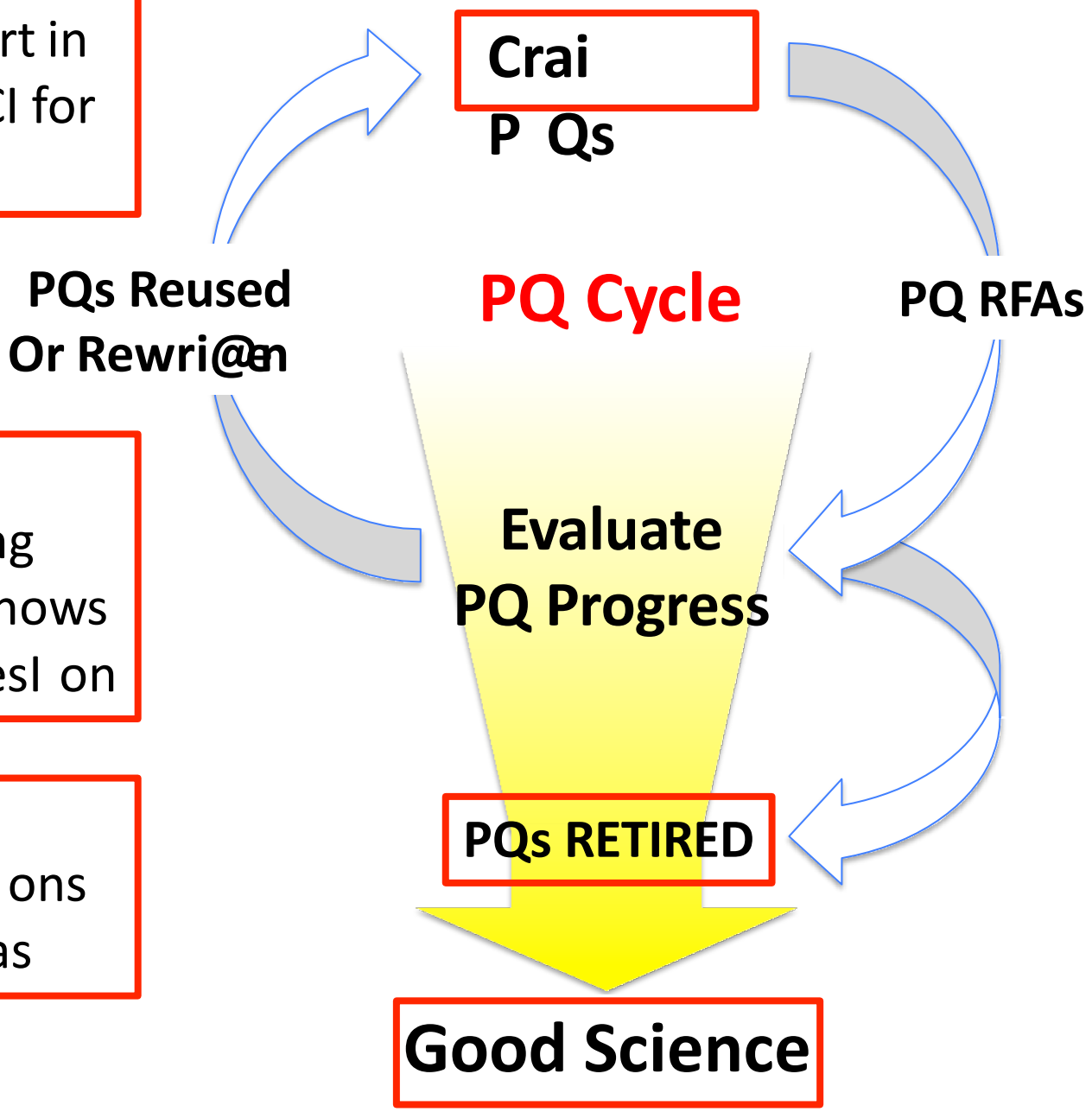
- Team determines customiz aI o n f o r each PQ
- Team responds to inquiries from potenI a l a p p l i cants
- Team determines which submia ed app’s are responsive to PQ
- Team follows progress of funded grants
- At end of RFA cycle, recommends if PQ is reused, rewria en, or reI red
- If reI red, then writes “close out” report
- If science needs a a enI o n , team directs conI n u ed a a enI o n (meeI n gs or other new resources)

3 SUGGESTED METRICS

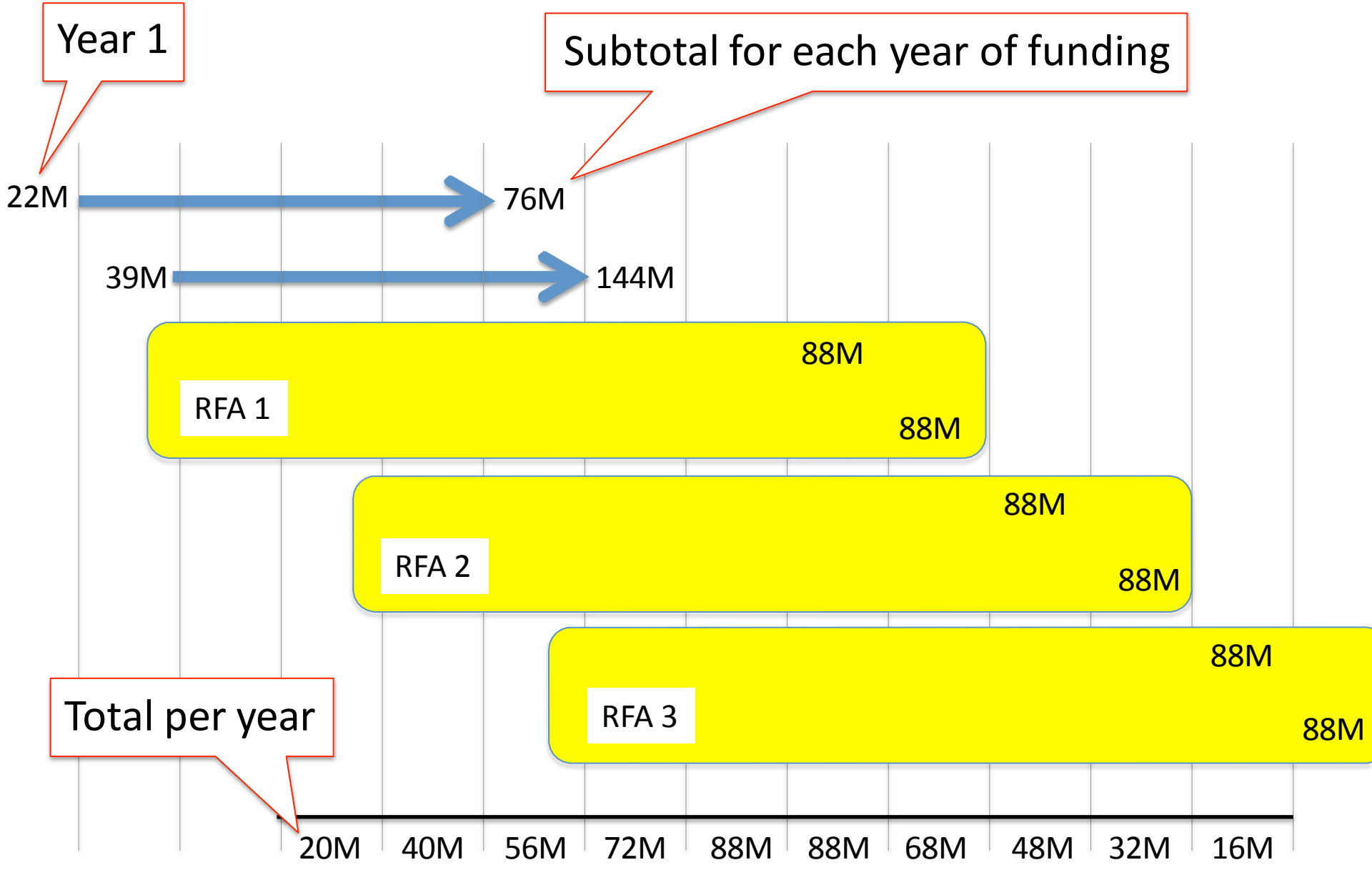
1.Short term:
Enthusiasl c support in community and NCI for developing PQs

2. Mid term:
Good rate of rel ring PQs (now ~40%); shows good a a ack on quesl on

3. Long term:
Top level contribul ons in PQ research areas



Budget Projec' ons



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To raise new questions, new possibilities, to regard old problems from a new angle, requires creative imagination and marks real advance in science.

Einstein and Infeld. in The EvoluIon of Physics. *1938.*