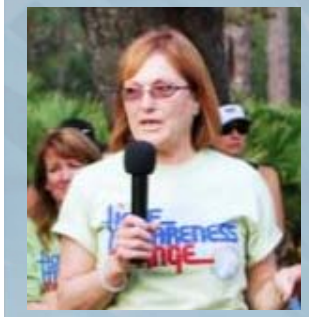
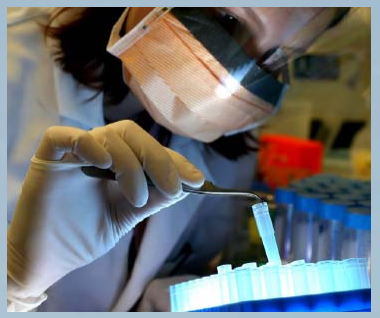
The Congressionally Directed Medical Research Programs

A Storyboard Approach to Charting Research Progress and Demonstrating Impact

Naba Bora, Ph.D.
Program Manager




CDMRP
Department of Defense

Outline

- CDMRP Overview
- NFRP Overview
- NF Storyboard

CUTTING EDGE RESEARCH

CDMRP
Department of Defense

WHO is the CDMRP?

Department of Defense

Department of the Army

Army Medical Command

Medical Research and Materiel Command

Congressionally Directed Medical Research Programs

CDMRP
Department of Defense

Consumers

- **Grassroots consumers heightened political awareness of breast cancer that led to increased funding for cancer research and the 1992 creation of the CDMRP. The voices and experiences of consumers continue to play a pivotal role in the establishment and growth of research programs.**

Over 2,100 consumers representing over 1,000 organizations have served on Peer Review and Programmatic Review panels

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FY16 Funding

Program	$M		Program	$M
Alcohol and Substance Abuse Disorders	$4.0		Peer Reviewed Alzheimer's	$15.0
Amyotrophic Lateral Sclerosis	$7.5		Peer Reviewed Cancer (13 Topics)	$50.0
Autism	$7.5		Peer Reviewed Medical (39 Topics)	$278.7
Bone Marrow Failure	$3.0		Peer Reviewed Orthopaedic	$30.0
Breast Cancer	$120.0		Prostate Cancer	$80.0
Duchenne Muscular Dystrophy	$3.2		Reconstructive Transplant	$12.0
Epilepsy	$7.5		Spinal Cord Injury	$30.0
Gulf War Illness	$20.0		Tick-Borne Disease	$5.0
Joint Warfighter Medical*	$50.0		Trauma Clinical Research	$10.0
Lung Cancer	$12.0		Tuberous Sclerosis Complex	$6.0
Military Burn	$8.0		Vision	$10.0
Multiple Sclerosis	$6.0			
Neurofibromatosis	$15.0		Programs Managed on behalf of Others:	
Neurotoxin Exposure Treatment Parkinson's	$16.0		Defense Medical R&D*	$299.6
Orthotics and Prosthetics Outcomes	$10.0		Defense Medical R&D Restoral*	207.5
Ovarian Cancer	$20.0		Psychological Health and Traumatic Brain Injury*	$125.0

* CDMRP is assisting with the management of a specified portion of a larger appropriation(s)

TOTAL = $1.468B

Vision and Mission

Vision

Transform healthcare for Service Members and the American public through innovative and impactful research

Mission

Responsibly manage collaborative research that discovers, develops, and delivers health care solutions for Service Members, Veterans and the American public

Hallmarks

- **Targeted research funds added to DoD budget by Congress**
- **Consumers participate throughout process**
- **National Academy of Medicine (IOM) recommended model for application review**
- **Funds high-impact innovative research**
- **Each program's vision and investment strategy are adapted annually, allowing rapid response to changing needs**
- **Avoid Duplication with other funding agencies**
  - Fills Unfunded/Unmet Gaps
- **Funding flexibility**
  - Funds obligated up-front; limited out-year budget commitments
  - Limited continuation funding
  - No "pay line;" funding recommendations based on portfolio composition, adherence to intent of mechanism, relative impact in addition to technical merit

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Goal of the Two-Tier Review Process

Mission: **Responsibly manage collaborative research that discovers, develops, and delivers health care solutions for Service Members, Veterans and the American public.**

Peer Review	Partnership	Programmatic Review

- **Criterion-based evaluation of full proposal**
- **Determination of "absolute" scientific merit**
- **Outcome: Written critique and scores for individual criteria and overall merit**
  - No standing peer review panels
  - No contact between reviewers and applicants

- **Comparison among proposals of high scientific merit**
- **Determination of adherence to intent and program relevance**
- **Outcome: Funding recommendations**
  - No "pay line" (portfolio balance)
  - Funds obligated up front; no out-year budget commitments (but milestones imposed)
  - No continuation funding

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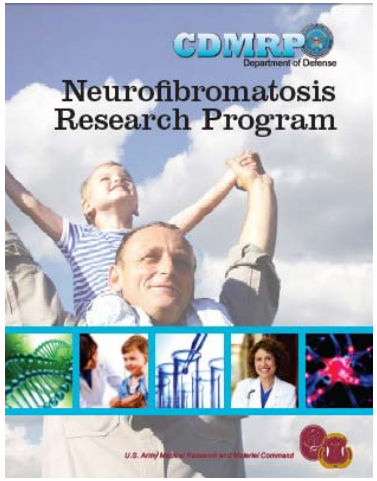
Neurofibromatosis Research Program



Vision

Decrease the clinical impact of neurofibromatosis

Mission

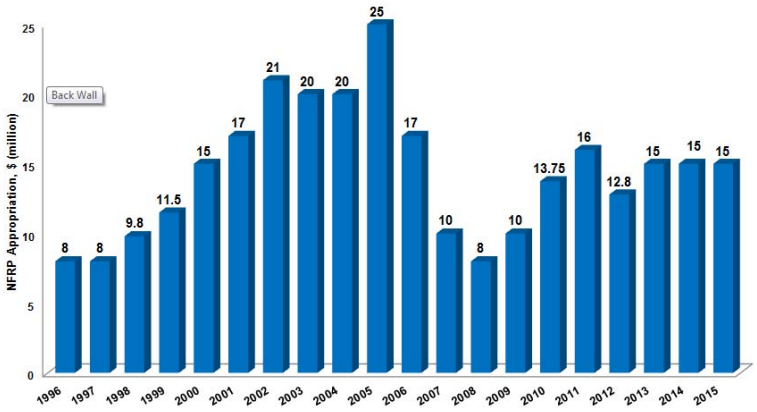
Promote research directed toward the understanding, diagnosis, and treatment of NF1, NF2 and Schwannomatosis to enhance the quality of life for persons with those diseases.

Key Facts

$287.85 million in FY96-14
332 awards in FY96-14
20 awards recommended for funding in FY15

Mechanisms supported: **Clinical Trials, Consortium, Investigator Initiated , New Investigator, Exploration Hypothesis Development**

Funding History



US Army Medical Research and Materiel Command

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What is Neurofibromatosis?

Genetic disorder causes tumors to grow along various types of nerves.
Classified as a rare disorder but more Common than Cystic fibrosis, Muscular Dystrophy, Huntington's' disease and Tay Sachs combined

NF1

- Von Recklinghausen NF
- Peripheral NF
- 1 in 3,000 births
- Autosomal dominant
- 50% sporadic, 50% genetic
- Neurofibromas under/on skin,
- Enlargement and deformation of bones and curvature of spine
- Tumors in brain, cranial nerves or spinal cord
- 50% have learning disabilities

NF2

- Bilateral Acoustic NF (BAN)
- 1:25,000
- Multiple tumors on cranial and spinal nerves
- Lesions on brain and spinal cord
- Tumors on both auditory nerves
- Hearing loss in teens/twenties first symptom

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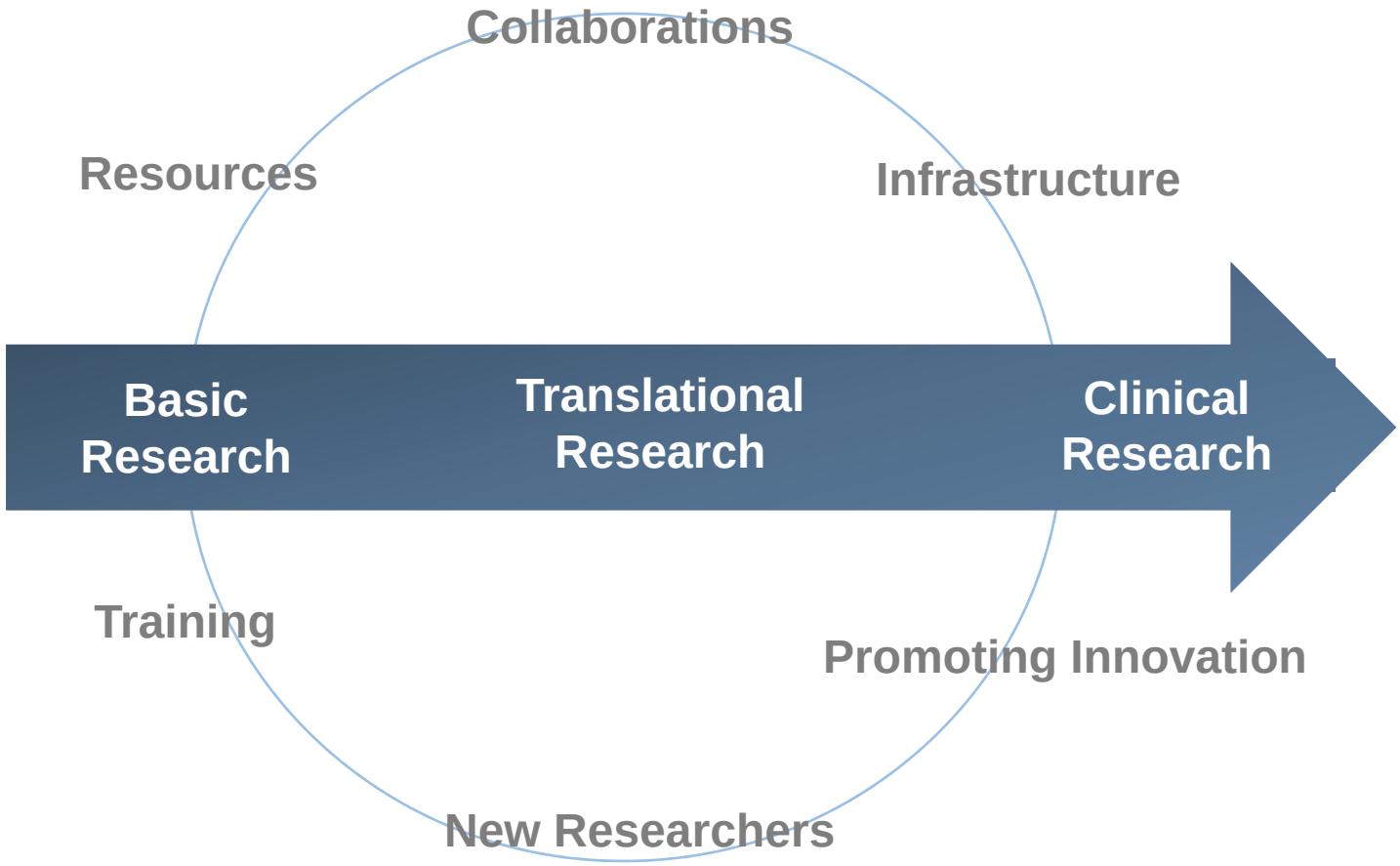
NFRP Strategy
Moving the field forward



Measuring Impact

- Return on Investment
- Research Outcomes- Publication, patents
- Research Products- Drugs, devices
- Evaluate collaborations created
- New investigators recruited and retained
- Storyboards

NF Storyboards

Goals:

1. Identify gaps in research funding
2. Access impact of NFRP funding
3. ID key advances in NF in visual format

Audience:

1. Consumers (patients and advocates)
2. Congress
3. Programmatic panel
4. CDMRP

NF Storyboards

Ongoing program evaluation effort at the CDMRP, the NFRP has developed NF1 and NF2 "story boards" identifying key research advances in the fields of NF1 and NF2 through the years.

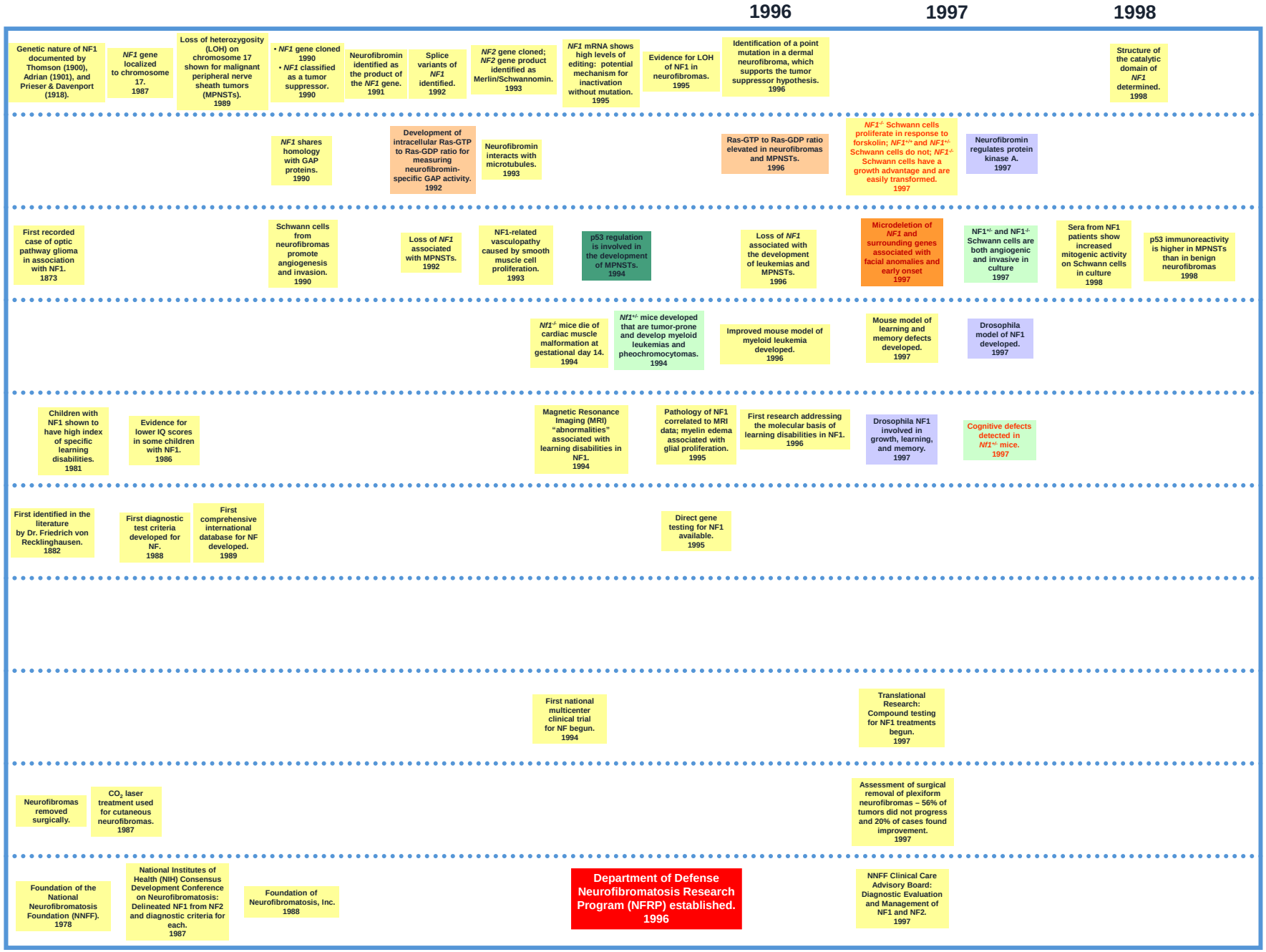
NF Storyboards

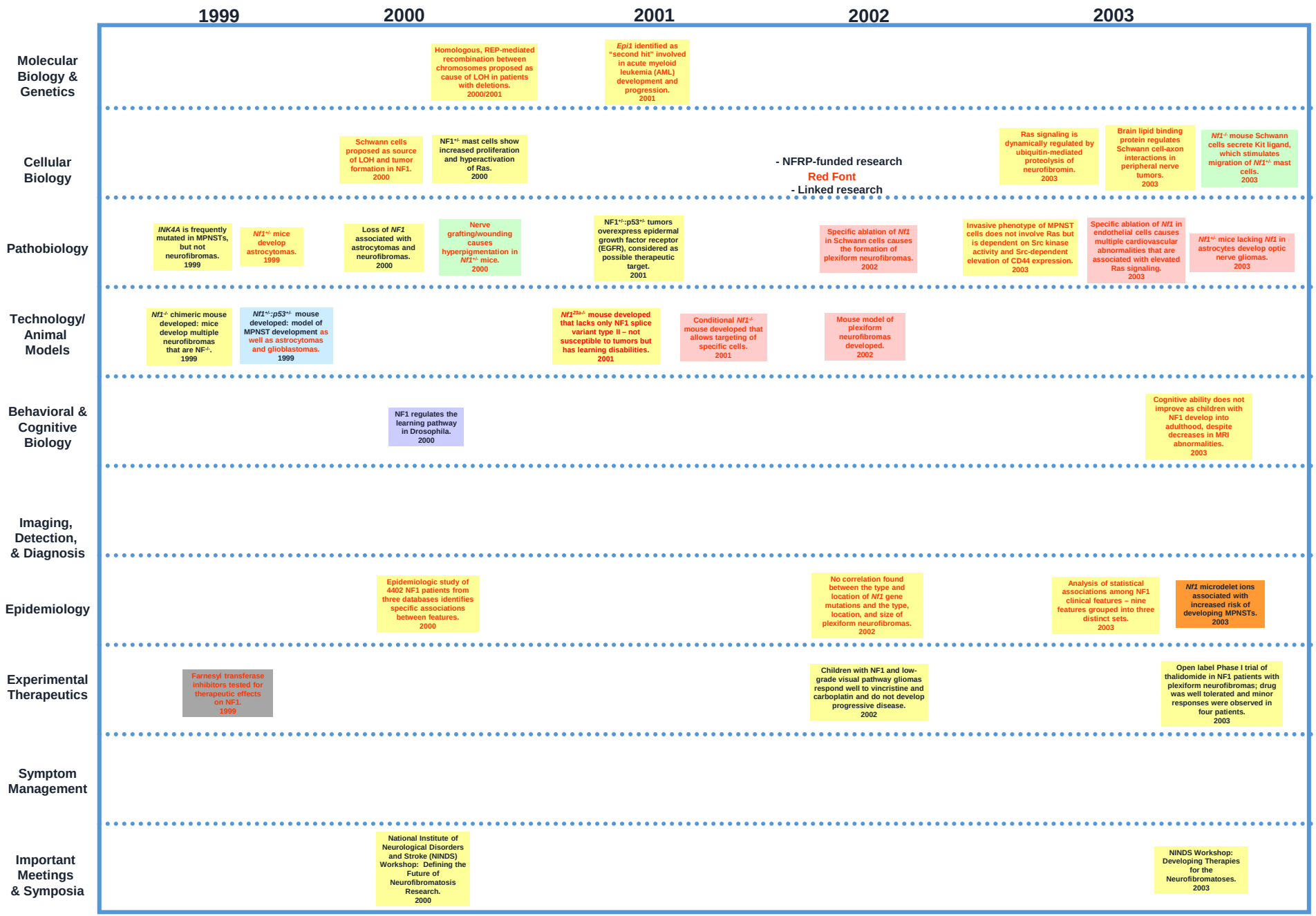
Process :

1. Identified key research advances from publications, regardless of source of funding
2. Identified NFRP research project results
3. Mapped each advancement to year
4. Mapped to specific area of science
   - (i.e.) Molecular biology, genetics, cell biology, pathobiology
5. Mapped to disease type (NF1
   - NF1 or NF2
6. Color coded for links between research

Neurofibromatosis Type 1 (NF1)

- Linked research
Red Font - NFRP-funded research




1999
2000
2001
2002
2003
Molecular Biology & Genetics
Cellular Biology
Pathobiology
Technology/ Animal Models
Behavioral & Cognitive Biology
Imaging, Detection, & Diagnosis
Epidemiology
Experimental Therapeutics
Symptom Management
Important Meetings & Symposia
Homologous, REP-mediated recombination between chromosomes proposed as cause of LOH in patients with deletions. 2000/2001
Epi1 identified as "second hit" involved in acute myeloid leukemia (AML) development and progression. 2001
Schwann cells proposed as source of LOH and tumor formation in NF1. 2000
NF1+/- mast cells show increased proliferation and hyperactivation of Ras. 2000
- NFRP-funded research
Red Font
- Linked research
Ras signaling is dynamically regulated by ubiquitin-mediated proteolysis of neurofibromin. 2003
Brain lipid binding protein regulates Schwann cell-axon interactions in peripheral nerve tumors. 2003
Nf1-/- mouse Schwann cells secrete Kit ligand, which stimulates migration of Nf1+/- mast cells. 2003
INK4A is frequently mutated in MPNSTs, but not neurofibromas. 1999
Nf1+/- mice develop astrocytomas. 1999
Loss of Nf1 associated with astrocytomas and neurofibromas. 2000
Nerve grafting/wounding causes hyperpigmentation in Nf1+/- mice. 2000
NF1+/-:p53+/- tumors overexpress epidermal growth factor receptor (EGFR), considered as possible therapeutic target. 2001
Specific ablation of Nf1 in Schwann cells causes the formation of plexiform neurofibromas. 2002
Invasive phenotype of MPNST cells does not involve Ras but is dependent on Src kinase activity and Src-dependent elevation of CD44 expression. 2003
Specific ablation of Nf1 in endothelial cells causes multiple cardiovascular abnormalities that are associated with elevated Ras signaling. 2003
Nf1+/- mice lacking Nf1 in astrocytes develop optic nerve gliomas. 2003
Nf1-/- chimeric mouse developed: mice develop multiple neurofibromas that are NF-/-. 1999
Nf1+/-:p53+/- mouse developed: model of MPNST development as well as astrocytomas and glioblastomas. 1999
Nf123a-/- mouse developed that lacks only NF1 splice variant type II – not susceptible to tumors but has learning disabilities. 2001
Conditional Nf1-/- mouse developed that allows targeting of specific cells. 2001
Mouse model of plexiform neurofibromas developed. 2002
NF1 regulates the learning pathway in Drosophila. 2000
Cognitive ability does not improve as children with NF1 develop into adulthood, despite decreases in MRI abnormalities. 2003
Epidemiologic study of 4402 NF1 patients from three databases identifies specific associations between features. 2000
No correlation found between the type and location of Nf1 gene mutations and the type, location, and size of plexiform neurofibromas. 2002
Analysis of statistical associations among NF1 clinical features – nine features grouped into three distinct sets. 2003
Nf1 microdeletions associated with increased risk of developing MPNSTs. 2003
Farnesyl transferase inhibitors tested for therapeutic effects on NF1. 1999
Children with NF1 and low-grade visual pathway gliomas respond well to vincristine and carboplatin and do not develop progressive disease. 2002
Open label Phase I trial of thalidomide in NF1 patients with plexiform neurofibromas; drug was well tolerated and minor responses were observed in four patients. 2003
National Institute of Neurological Disorders and Stroke (NINDS) Workshop: Defining the Future of Neurofibromatosis Research. 2000
NINDS Workshop: Developing Therapies for the Neurofibromatoses. 2003

NF Storyboards

Findings:

1. More research advances in basic vs. clinical prior to 2004
   - » Most in area of molecular biology and genetics, cell biology and pathobiology, animal model development
2. NFRP has had an impact in shaping the progress of NF research
3. Gaps identified not necessarily a priority in NF research
4. Primarily a retrospective tool to look at program accomplishments
5. Not particularly useful for strategic decision making
6. Useful as a PR tool

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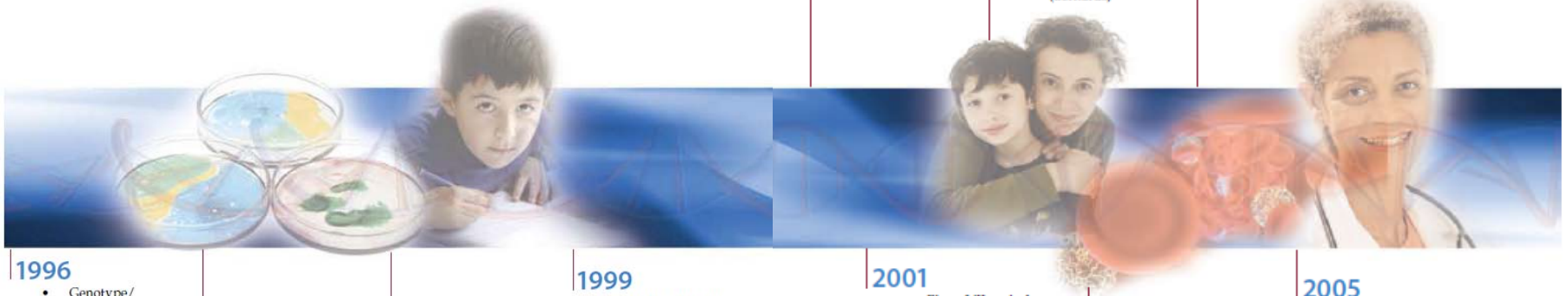
NFRP Research Milestones



1996
- Genotype/ phenotype analysis in NF1 (Friedman) and NF2 (MacCollin)
- Development of mouse models of NF1 and NF2 (Parada and Jacks)

1997
- Natural history studies of NF1 (Korf) and NF2 (Slattery)

1998
- Genetic evaluation of NF1 tumors (Viskochil)

1999
- Natural history of psychological aspects of NF1 (North)
- Preclinical evaluation of gene therapy for NF2 (Breakefield)
- Mouse models of NF (Shannon)

2000
- NF2 natural history consortium (Slattery)
- Phase II trial of R115777 for NF1 (Widemann)
- Gene expression profiling of NF1 (Ratner) and NF2 (Pulst) cells

2001
- Phase I/II trial of pirfenidone for NF1 (Packer)
- Development of oncolytic virus therapies (Rabkin)

2002
- Identification of the schwannomatosis locus (MacCollin)
- Studies of NF1 modifier genes (Bernards)

2003
- Generation of a new class of Ras inhibitors for NF1 (Kloog)
- Development of an HSV vector therapy for NF2 (Martuza)
- NF1 microarray consortium (Ratner)

2004
- Identifying Pak1 inhibitors as a treatment for NF2 (Peterson)
- Mouse models of NF (Shannon)

2005
- Phase II clinical trial of neoadjuvant chemotherapy for NF1 (Widemann)
- Statins for the treatment of NF1 cognitive deficits (Silva)
- Whole body MRI evaluation of NF1, NF2, and schwannomatosis patients (Plotkin)

2006
- NF clinical trials Consortium
- Oncolytic viral vectors for the treatment of NF1 (Rabkin)

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New Initiative: NFRP Mini Storyboards

Goals:

- Identify impact of NFRP on specific research topics
- Focus on current clinical trials
- Identify collaborations leading to clinical trials
- Show history of interventions

MEK Inhibitor Storyboard

- **MEK inhibitors - active area of research**
- **MEK inhibitors - act to inhibit MEK1 and/or MEK2**
- **Affects the MAPK/Erk pathway which is overactive in NF1 and certain cancers**
- **Currently in clinical trials**

QUESTION: What has been the impact of NFRPs funding of MEK studies

MEK Inhibitor Storyboard

Step 1

- **Identify Clinical Trials using MEK inhibitors**
- **Map to year and funding source on storyboard**

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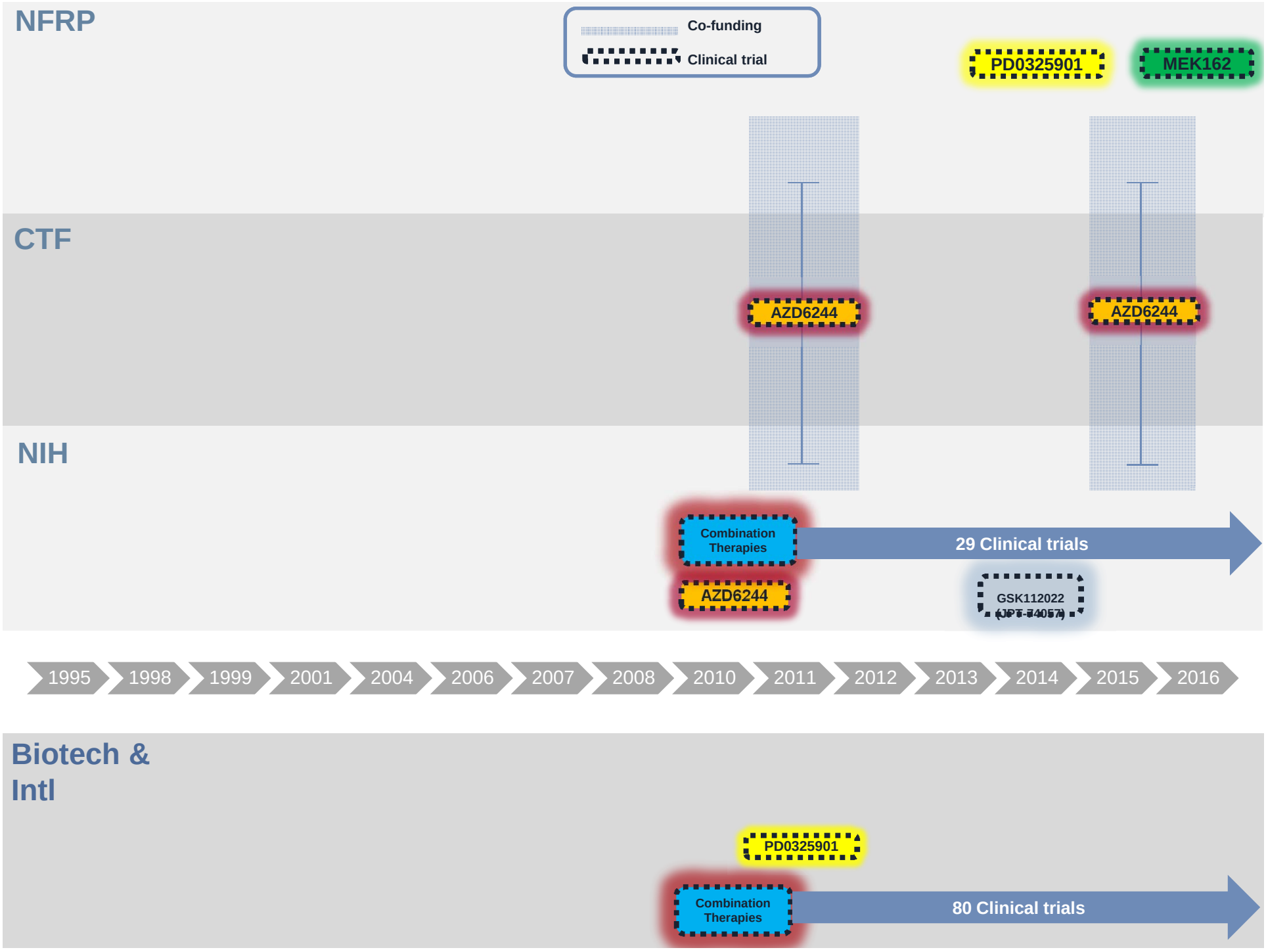
NFRP
Co-funding
Clinical trial
PD0325901
MEK162
CTF
AZD6244
AZD6244
NIH
Combination Therapies
29 Clinical trials
AZD6244
GSK112022
1995
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1999
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2004
2006
2007
2008
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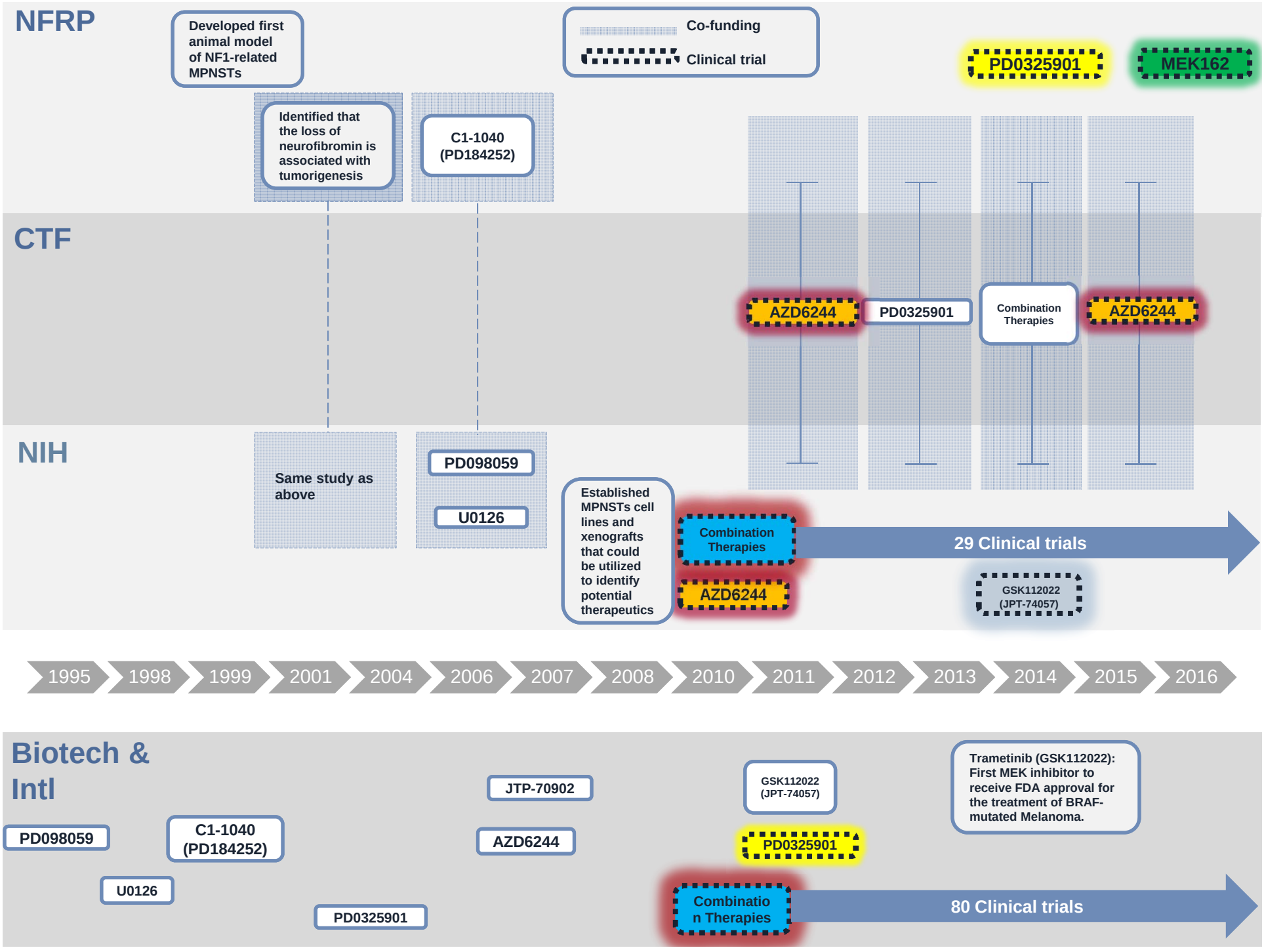
2011
2012
2013
2014
2015
2016
Biotech & Intl
PD0325901
Combination Therapies
80 Clinical trials

MEK Inhibitor Storyboard

Step 2

- Literature review of references for clinical trials
- Identify basic and preclinical studies that served as rational for MEK trials
- Map to storyboard


NFRP
Developed first animal model of NF1-related MPNSTs
Co-funding
Clinical trial
PD0325901
MEK162
Identified that the loss of neurofibromin is associated with tumorigenesis
C1-1040 (PD184252)
CTF
AZD6244
PD0325901
Combination Therapies
AZD6244
NIH
Same study as above
PD098059
U0126
Established MPNSTs cell lines and xenografts that could be utilized to identify potential therapeutics
Combination Therapies
AZD6244
29 Clinical trials
GSK112022 (JPT-74057)
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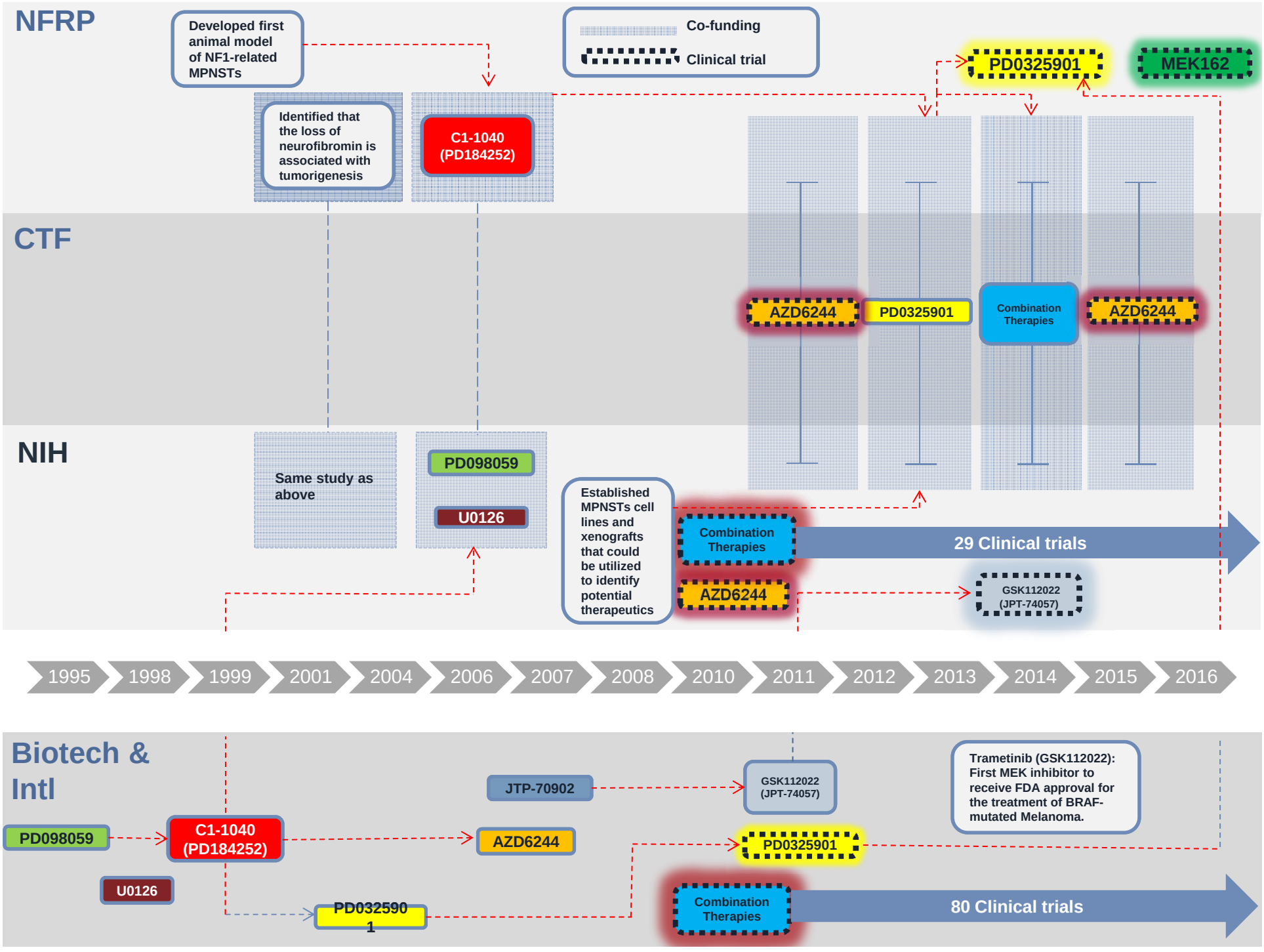
C1-1040 (PD184252)
U0126
PD0325901
JTP-70902
AZD6244
GSK112022 (JPT-74057)
PD0325901
Combinatio n Therapies
Trametinib (GSK112022): First MEK inhibitor to receive FDA approval for the treatment of BRAF-mutated Melanoma.
80 Clinical trials

MEK Inhibitor Storyboard

Step 3

- **Show how basic, preclinical and clinical trials are related**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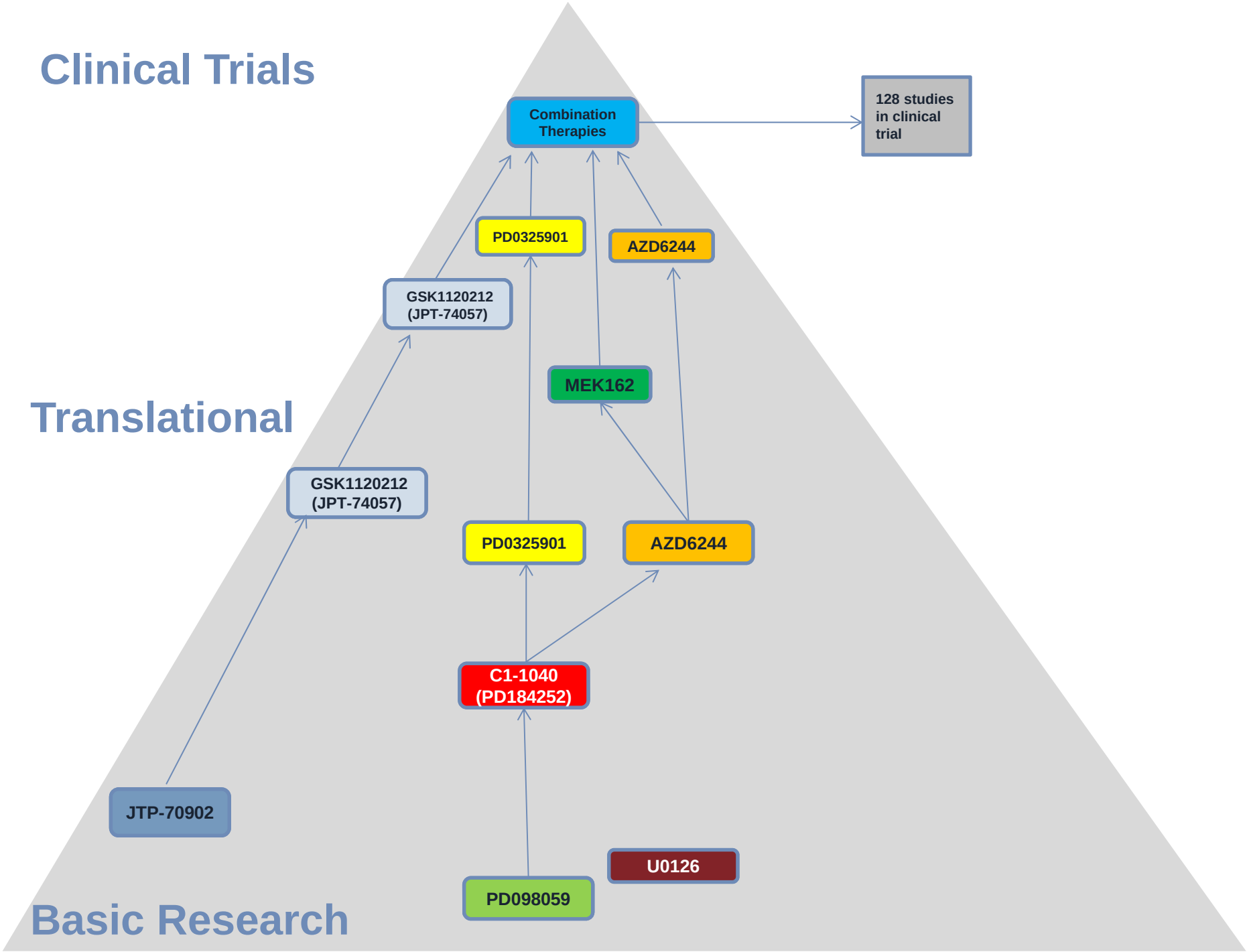
Clinical Trials
Translational
Basic Research
Combination Therapies
128 studies in clinical trial
PD0325901
AZD6244
GSK1120212 (JPT-74057)
MEK162
GSK1120212 (JPT-74057)
PD0325901
AZD6244
C1-1040 (PD184252)
JTP-70902
U0126
PD098059

MEK Inhibitor Storyboard

Conclusions

- **NFRP funded basic and preclinical studies have impacted current clinical trials with MEK inhibitors**

- **Funding from NFRP, CTF, NIH and Others were critical to the progress of MEK research currently in trials**

MEK Inhibitor Storyboard

Next Steps

- **Further analyze our findings**
- **Develop whitepaper**
- **Develop dynamic MEK storyboard using online tools**
  - **i.e Tiki-Toki (www.tiki-toki.com)**
- **Create additional storyboards for NF specific topics**

BRCA Storyboard

Breast Cancer Research Program

Ovarian Cancer Research Program

Contributions to advances in BRCA research

http://cdmrp.army.mil/brca_timeline/default.shtml

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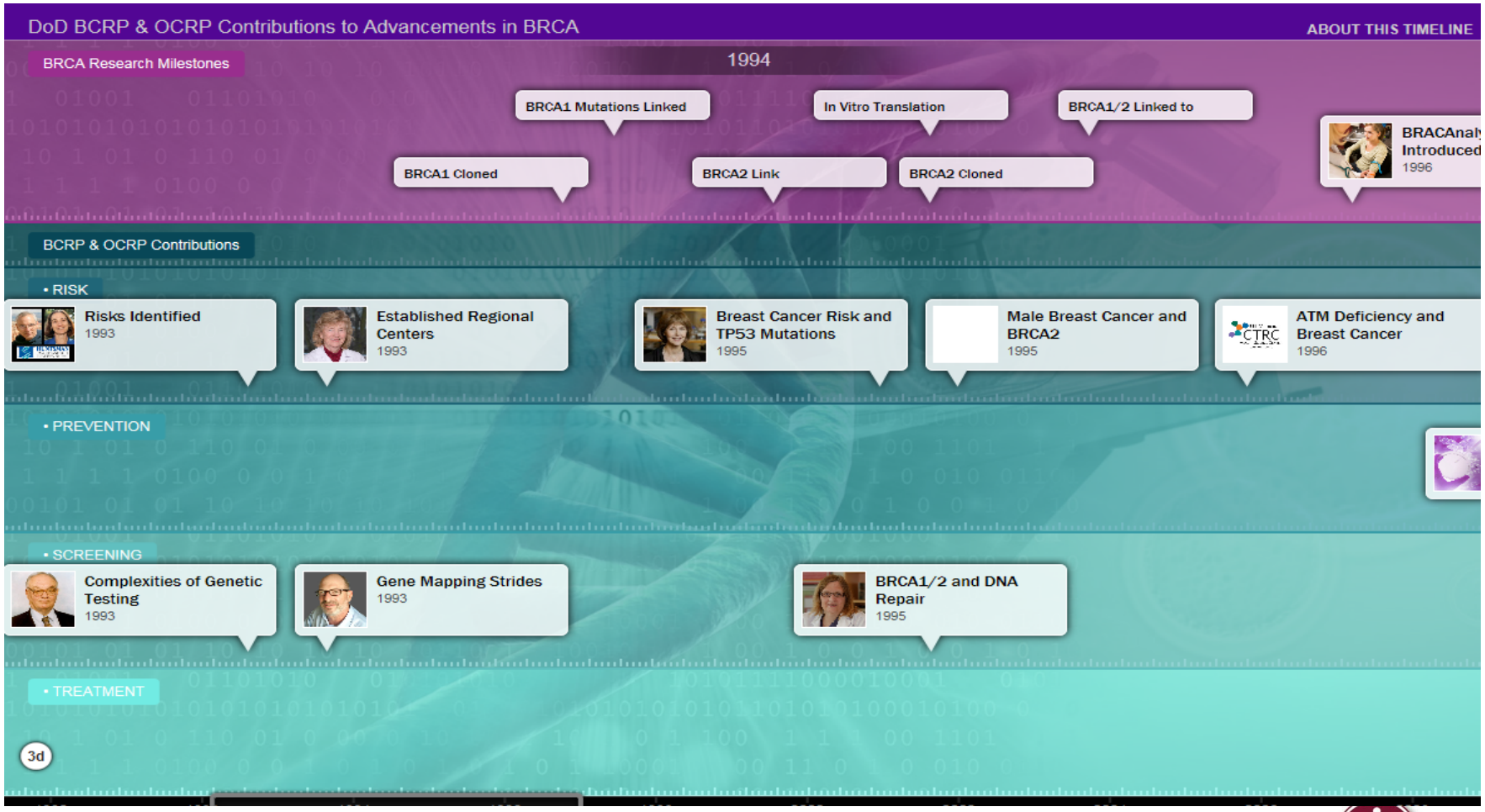
Advances in BRCA



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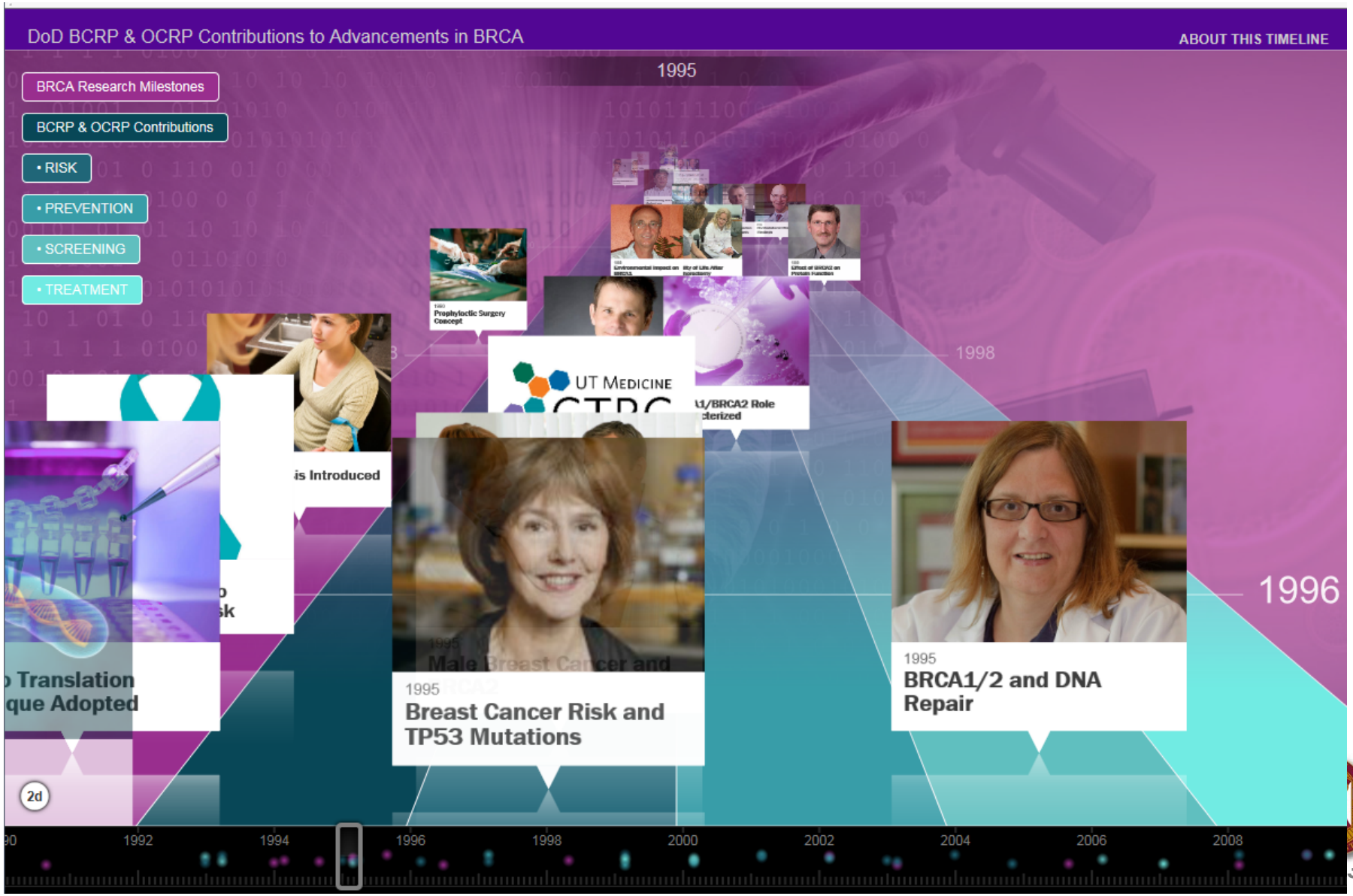
Advances in BRCA



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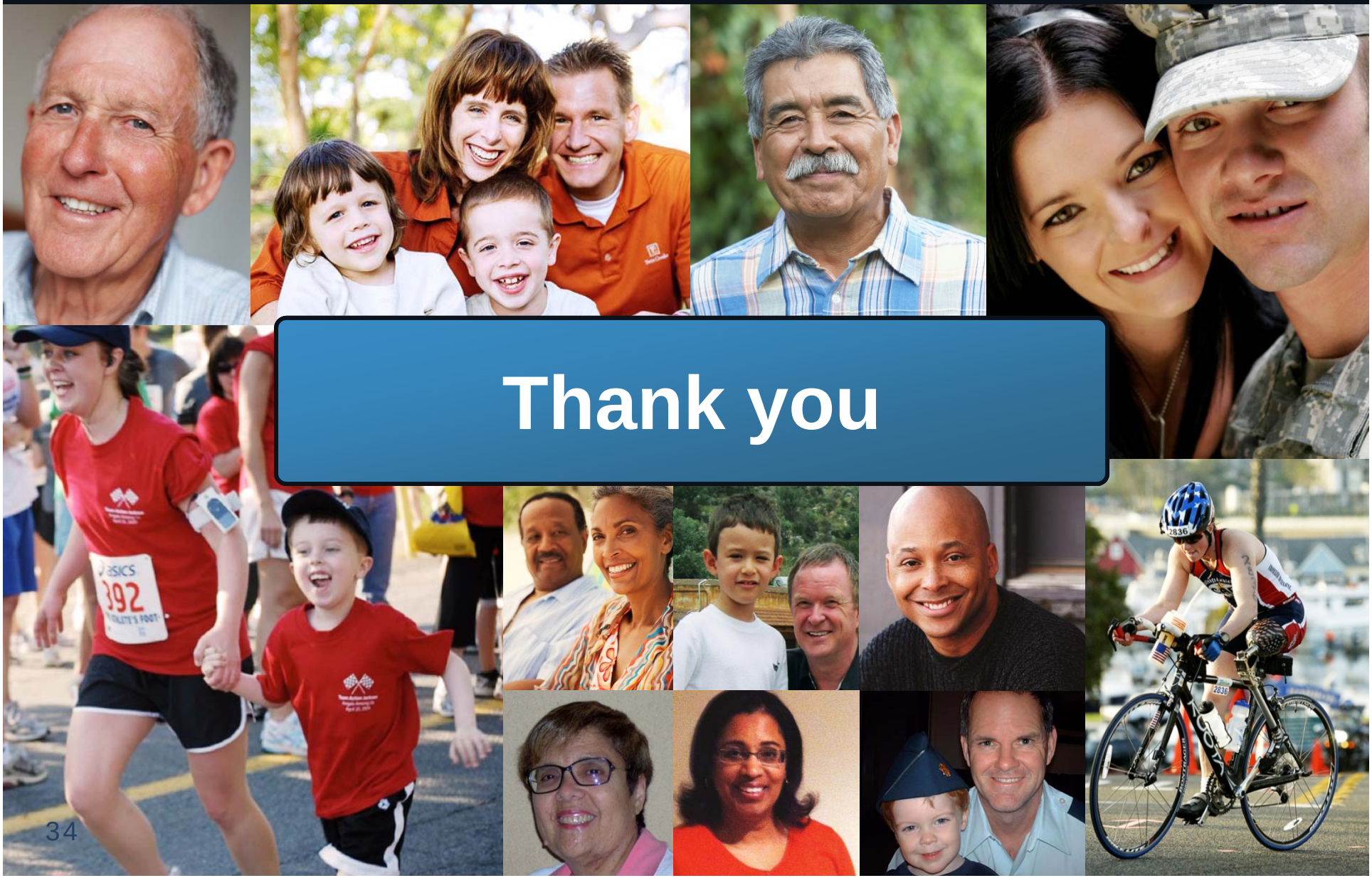
A Proud Consumer Legacy



Thank you