NCIC CTG Overview and Opportunities

Ralph Meyer

Director, NCIC CTG

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

NCIC Clinical Trials Group

A research organization

A cooperative clinical trials group

Previously funded by NCIC

Now funded by CCSRI

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National Cancer Institute of Canada: 1947-2009

- Non-governmental body supported by funds donated to:

  Canadian Cancer Society

  Terry Fox Foundation

- Supports a full spectrum of extramural (no intramural) cancer research
- Has supported national programs in epidemiology, clinical trials and behavioral research

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Canadian Cancer Society Research Institute

- In 2008, CCS determined that its research initiatives should be brought “in house” rather than being directed by a separate organization
- As a result, the CCSRI was formed
- The NCIC was absorbed into the CCSRI, and no longer exists as a separate research organization
- The CCSRI is funded by donations to CCS

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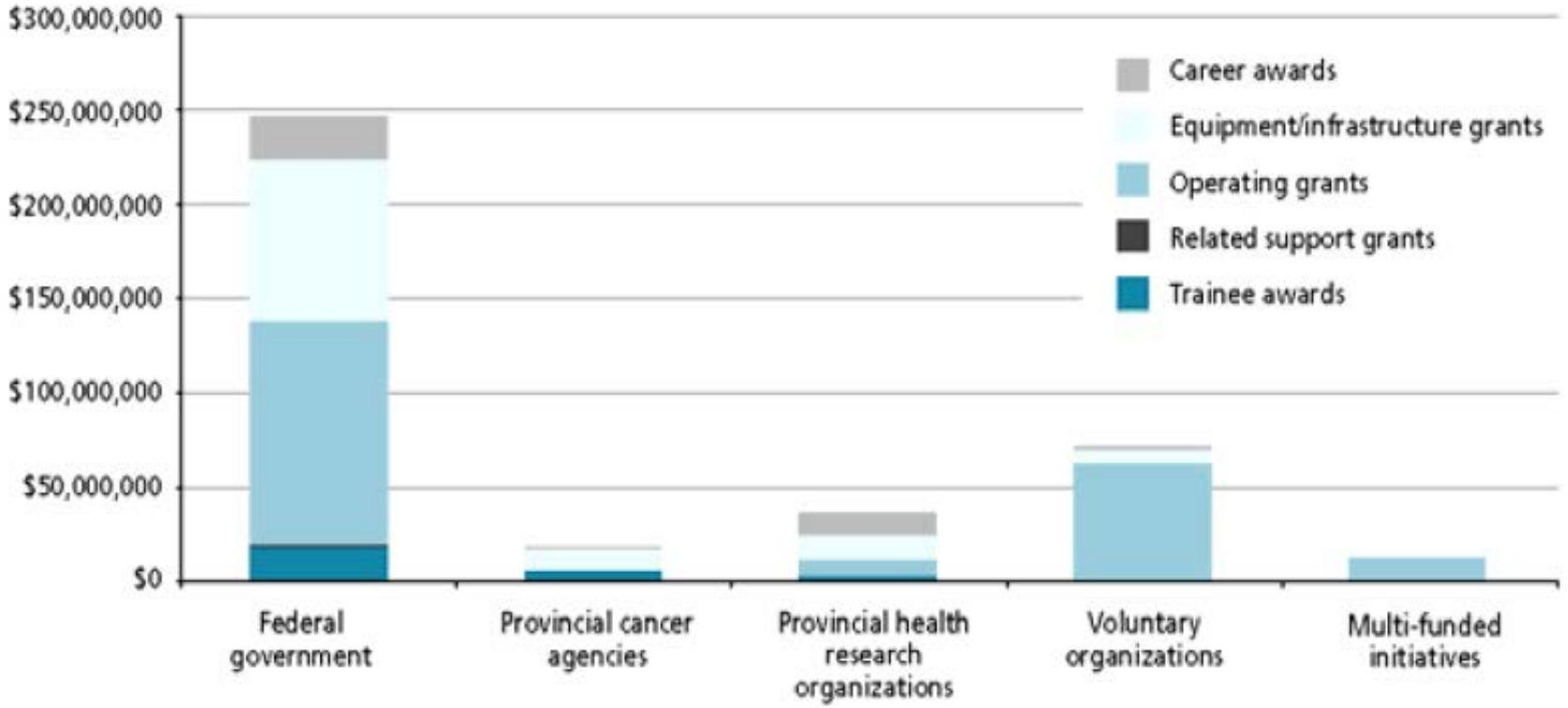
Funding

CCSRI

- **Funds:** operating grants
  program project grants
  personnel support awards
  other
- Funds two national networks / programs
  PROPEL
  ARCC
  NCIC CTG

FIGURE 3.1.1

2006 CANCER RESEARCH INVESTMENT BY FUNDING MECHANISM FOR EACH FUNDER SECTOR ($390.2M) [1]



[1] Refers to the sector of the organization that administered the funding program.

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CCRA, 2008: see http://www.ccra-acrc.ca/default_en.htm

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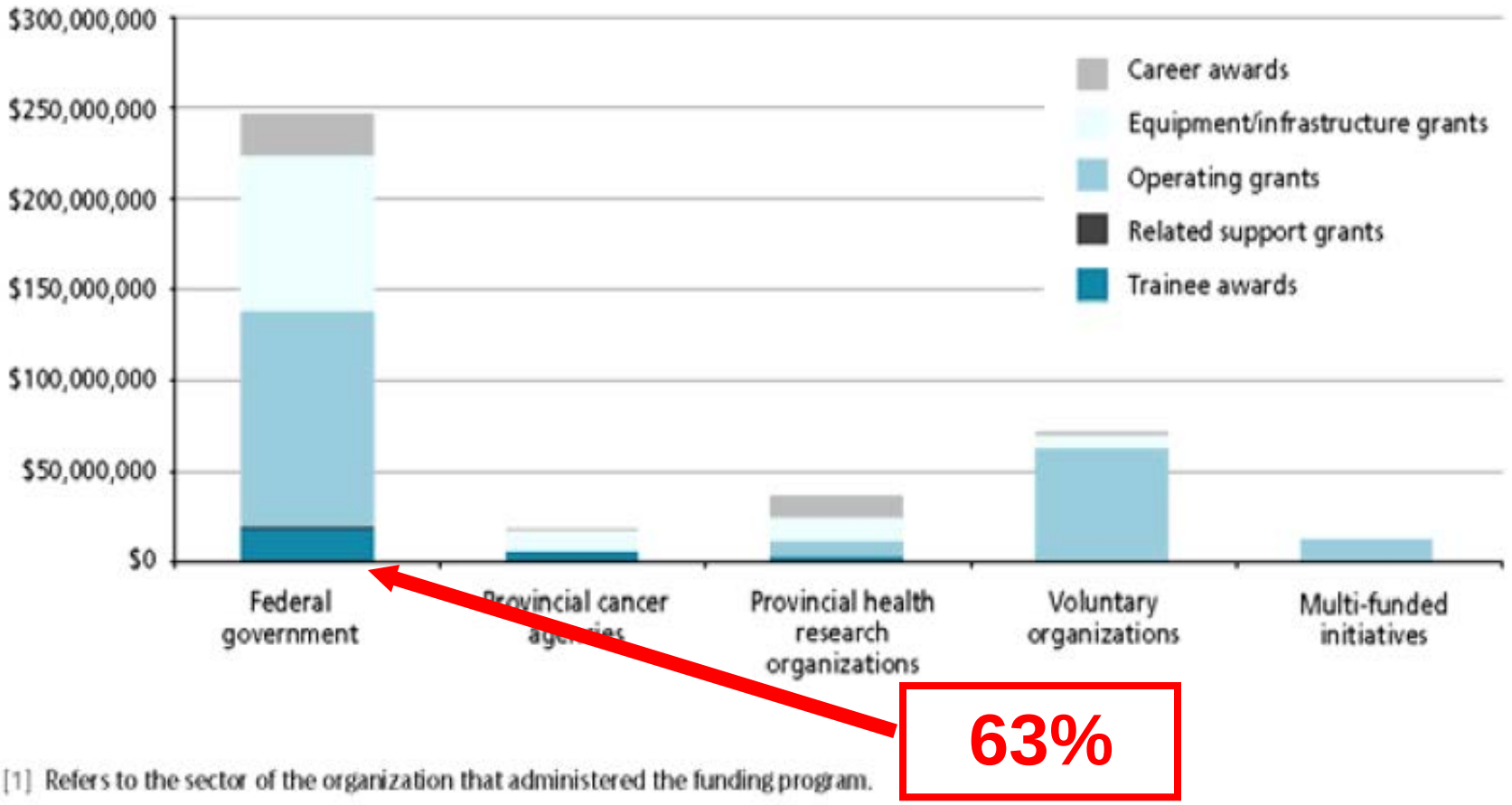

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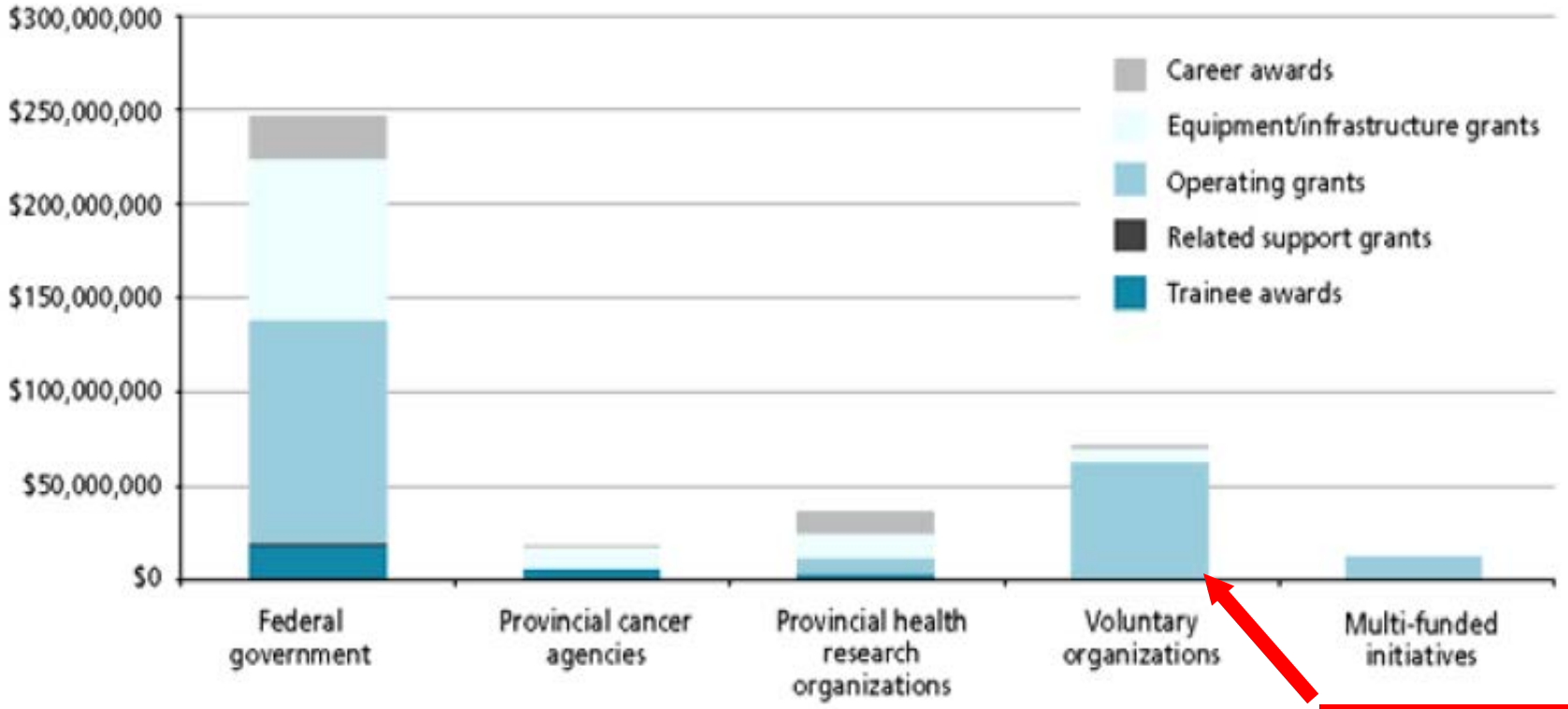

19%

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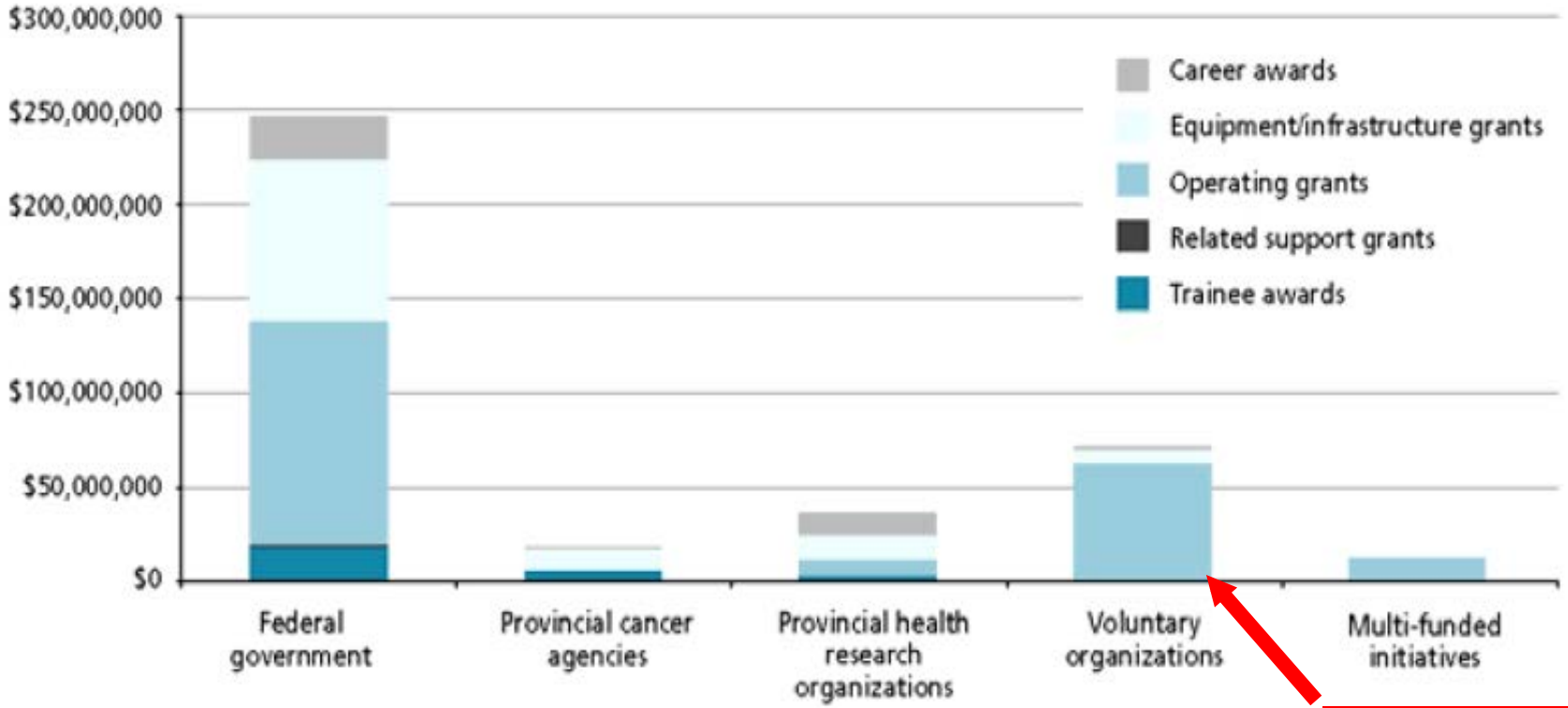

[1] Refers to the sector of the organization that administered the

CCS ~ 60% → **19%**

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CCRA, 2008: see http://www.ccra-acrc.ca/default_en.htm

Mission

The mission of the NCIC Clinical Trials Group (CTG) is to develop and conduct clinical trials aimed at improving the treatment and prevention of cancer with the ultimate goal of reducing morbidity and mortality from this disease.

NCIC Clinical Trials Group

- A research organization
- A clinical trials cooperative group
- Mandate is national
- Scope is international
- To include: all cancer disease sites
  all treatment modalities

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NCIC CTG: An Overview

- **1979:** NCIC decides to have formal group
- **1980:** CTG established in Kingston under Joe Pater
- **1982:** IND Program established
- **1988:** NIH funding received; formalized in 1997
- **1997:** Directions reviewed by NCIC Task Force on Clinical Studies
- **2006:** Recruitment of new Director
- **2010:** Pediatric IND Program established

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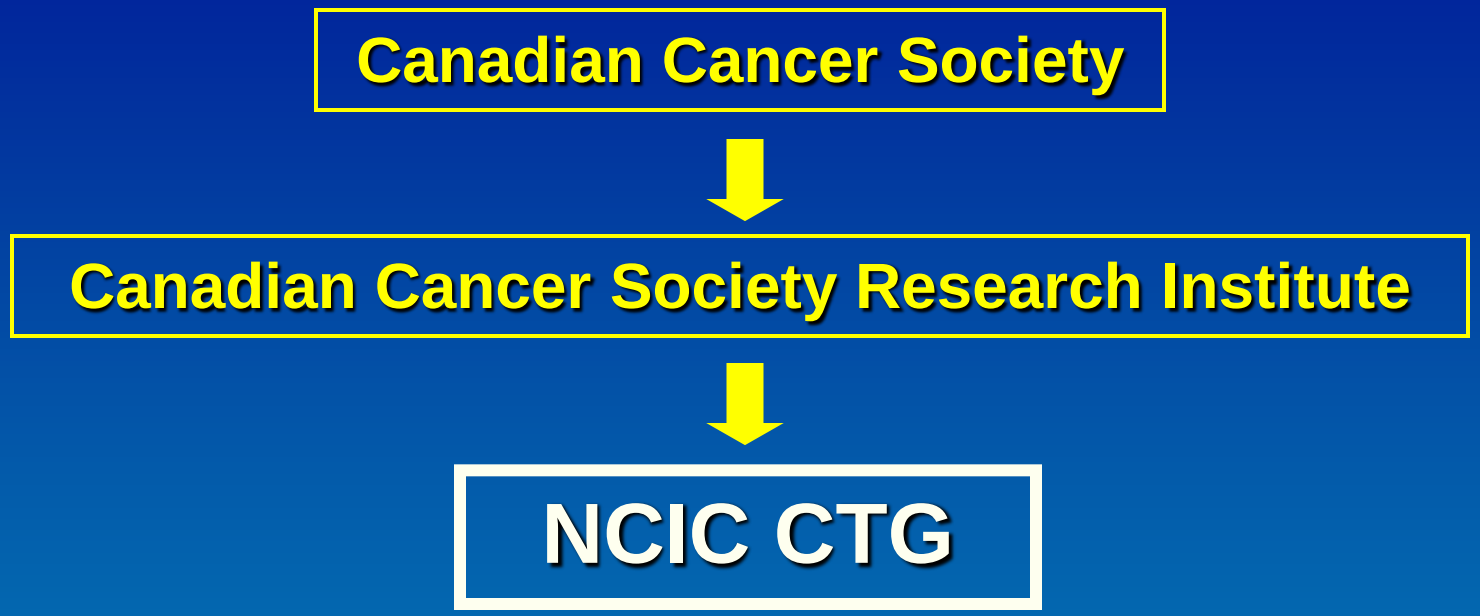
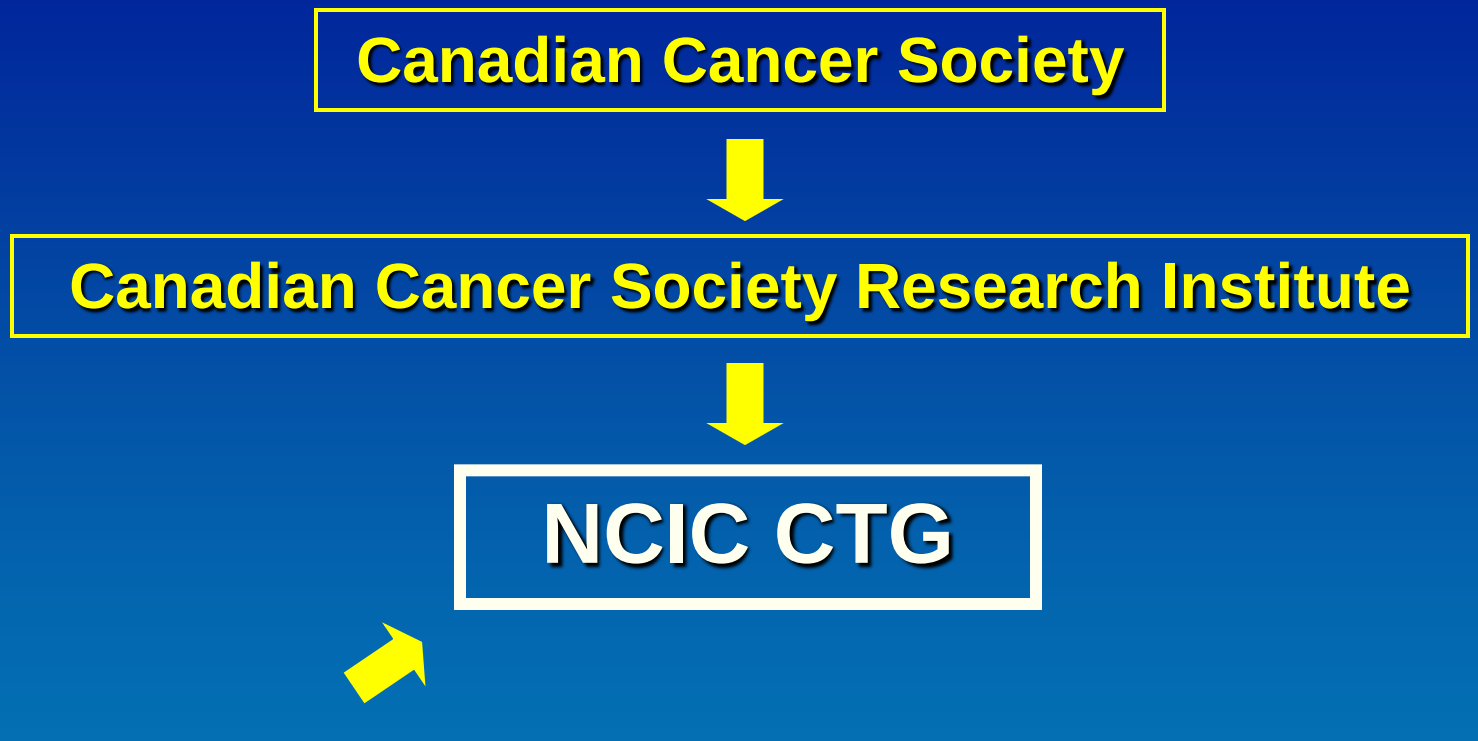
Funding

Funding


Canadian Cancer Society
Canadian Cancer Society Research Institute
NCIC CTG

Funding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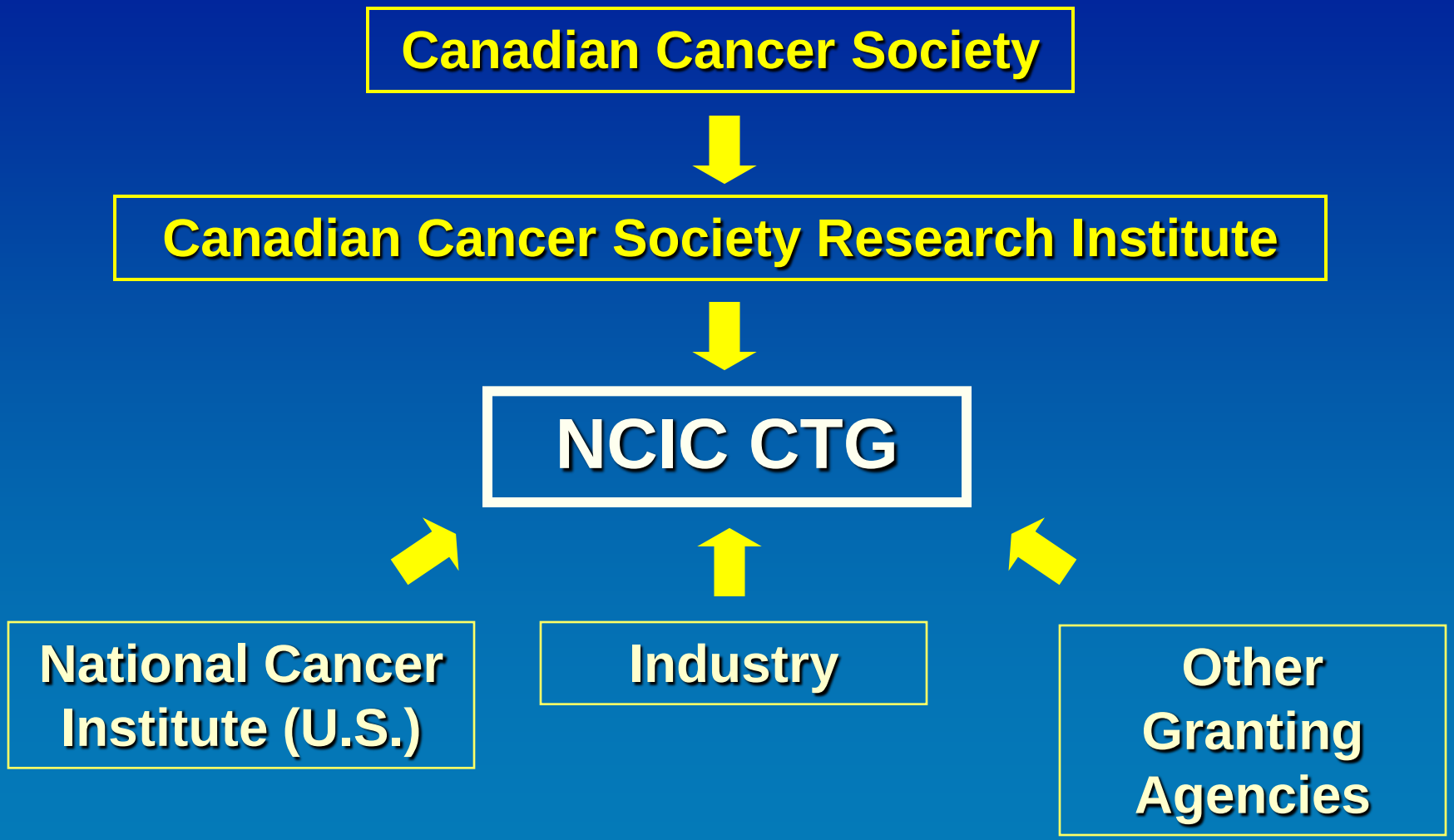
NCIC CTG
National Cancer Institute (U.S.)

Funding


Canadian Cancer Society
Canadian Cancer Society Research Institute
NCIC CTG
National Cancer Institute (U.S.)
Industry
Other Granting Agencies

Funding

CCSRI Funding of NCIC CTG:

- Program grant issued every 5 years
- Contingent on successful site review

  comprehensive grant submission

  site visit by external reviewers

  includes: scientific agenda

  methodology and data centre

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Funding

NCI (US):

- Program grant issued every 5 years
- Contingent on same criteria as NCIC / CCS, and:

  Leading initiatives with US groups

  Contributing to initiatives of US groups

  Includes correlative biology

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Funding

Other Granting Agencies:

- e.g., CIHR
  OICR
  Disease specific agencies
- Format varies: special opportunities
  companion questions
- In general, is project - specific

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Funding

Industry:

- Funding is project – specific
- Partner is pharmaceutical / biotech
- Often includes correlative biology
- Relationships include additional complexities

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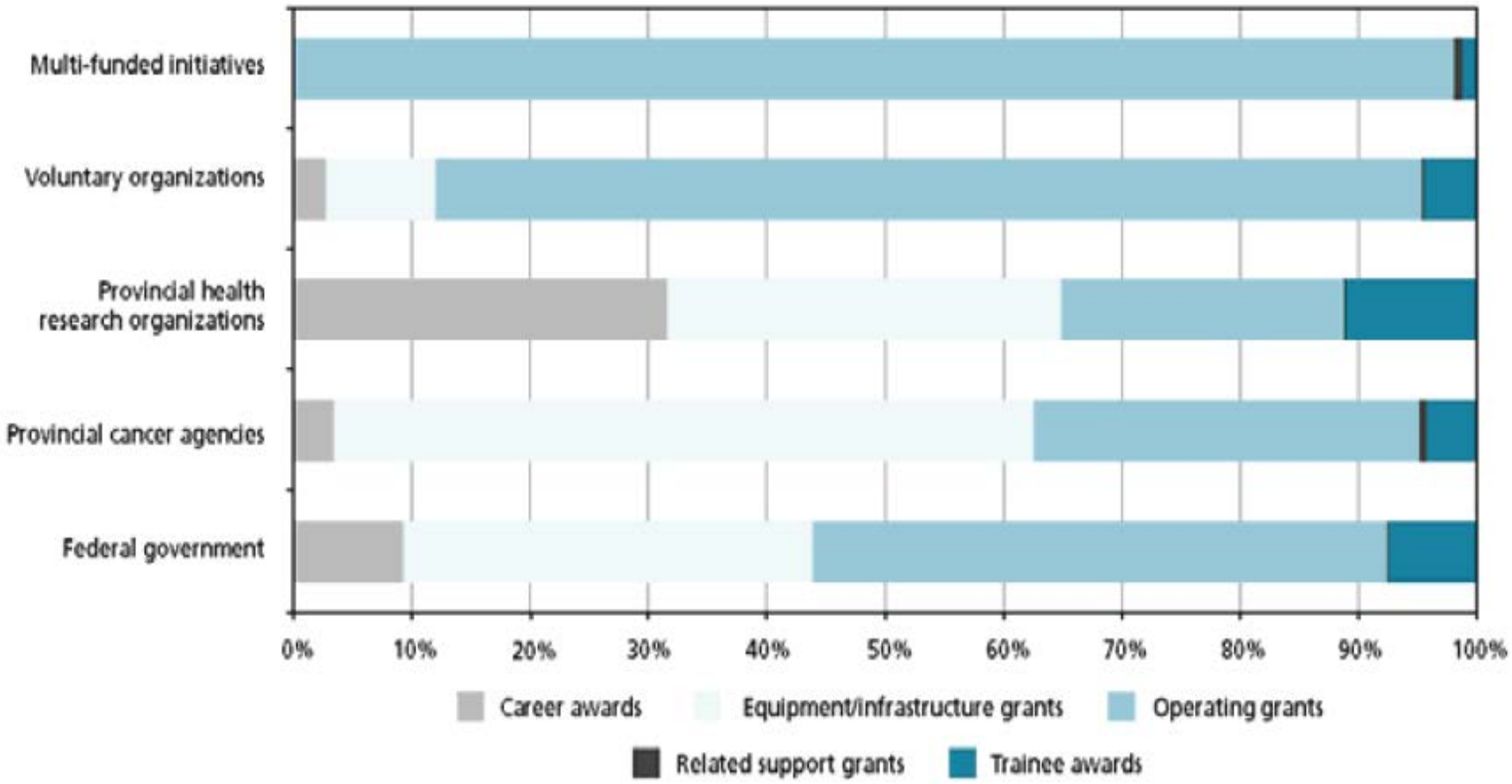
DISTRIBUTION OF 2006 CANCER RESEARCH INVESTMENT BY FUNDING MECHANISM FOR EACH FUNDER SECTOR [1]



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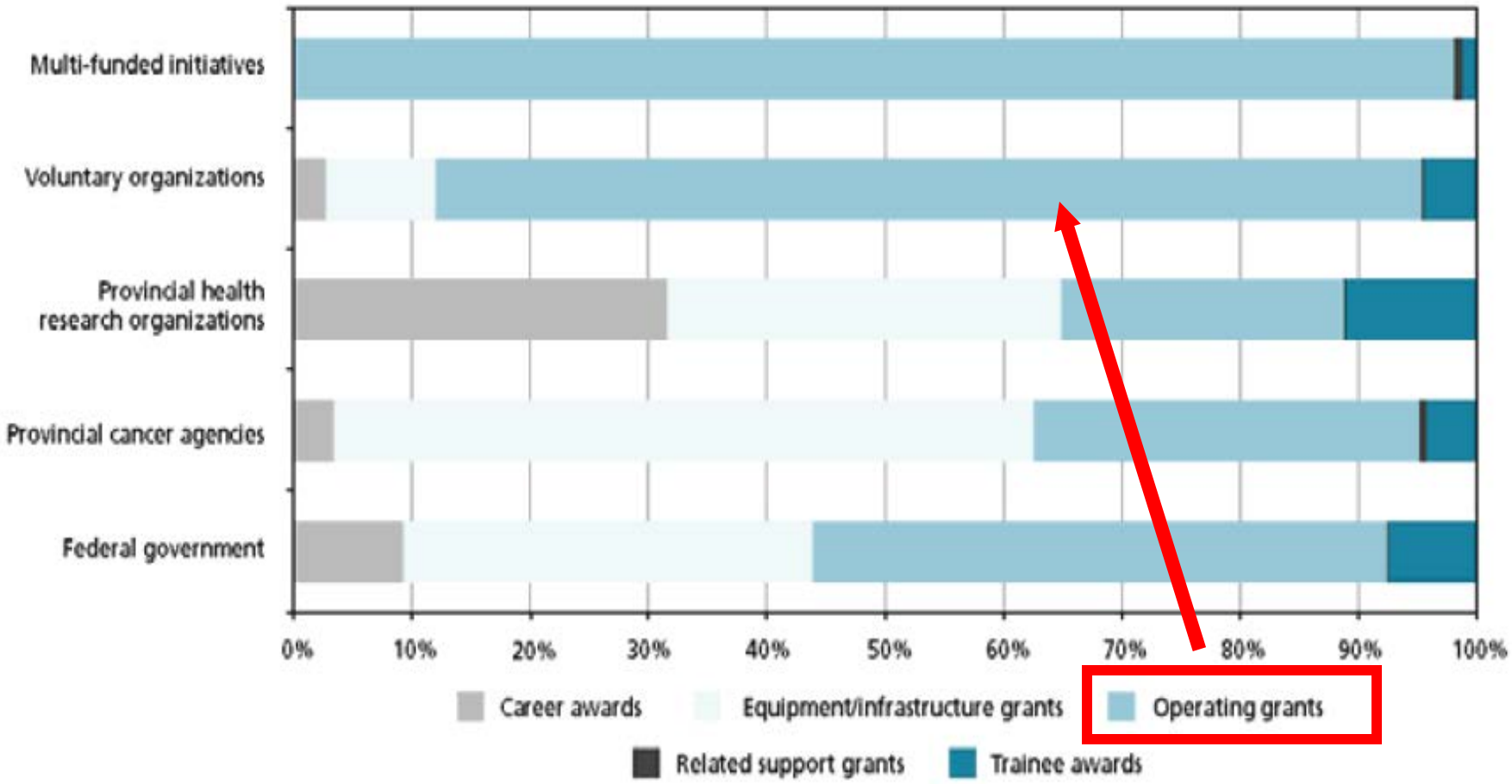

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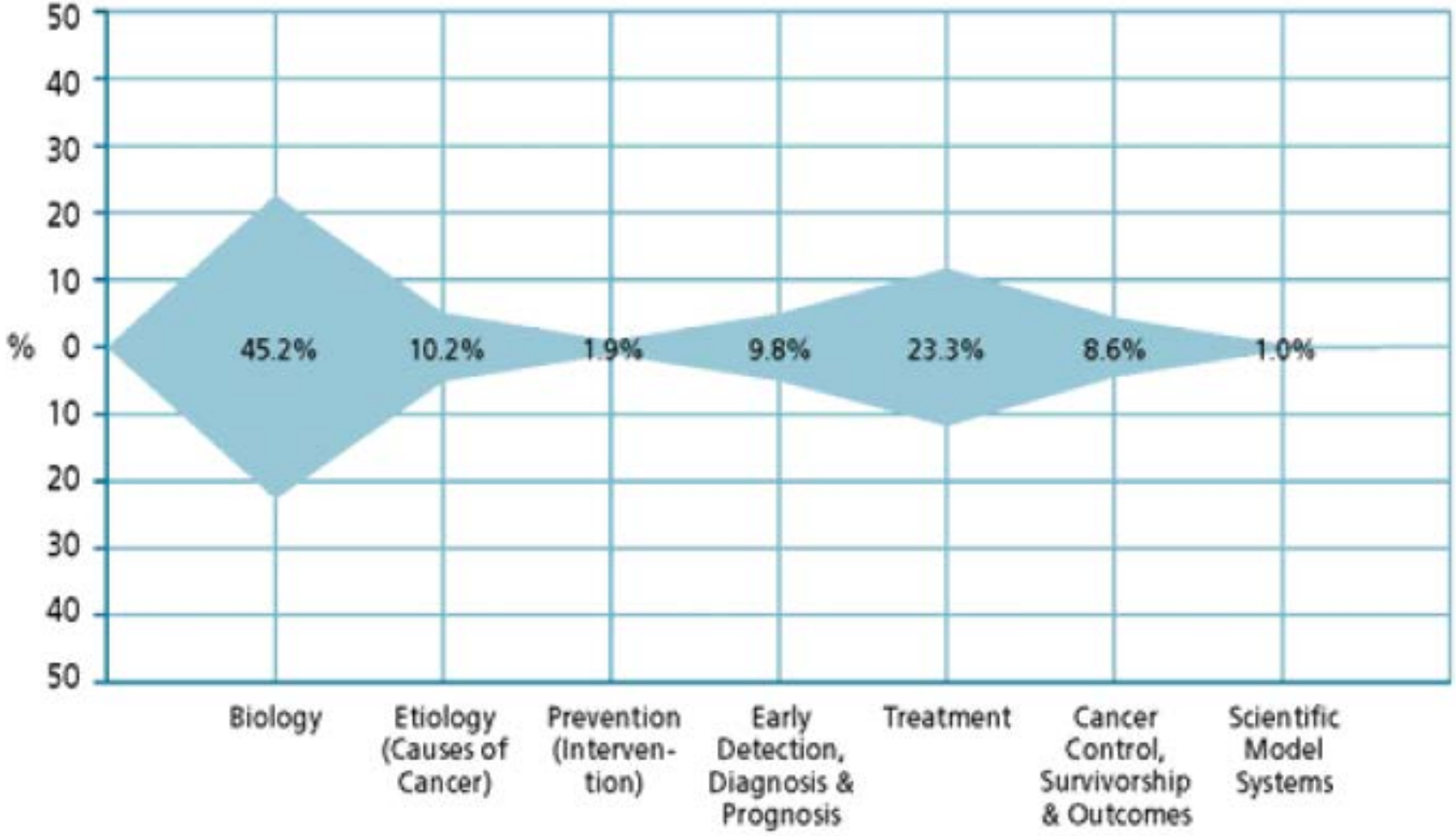
DISTRIBUTION OF 2006 CANCER RESEARCH INVESTMENT BY CSO CATEGORY ($390.2M)



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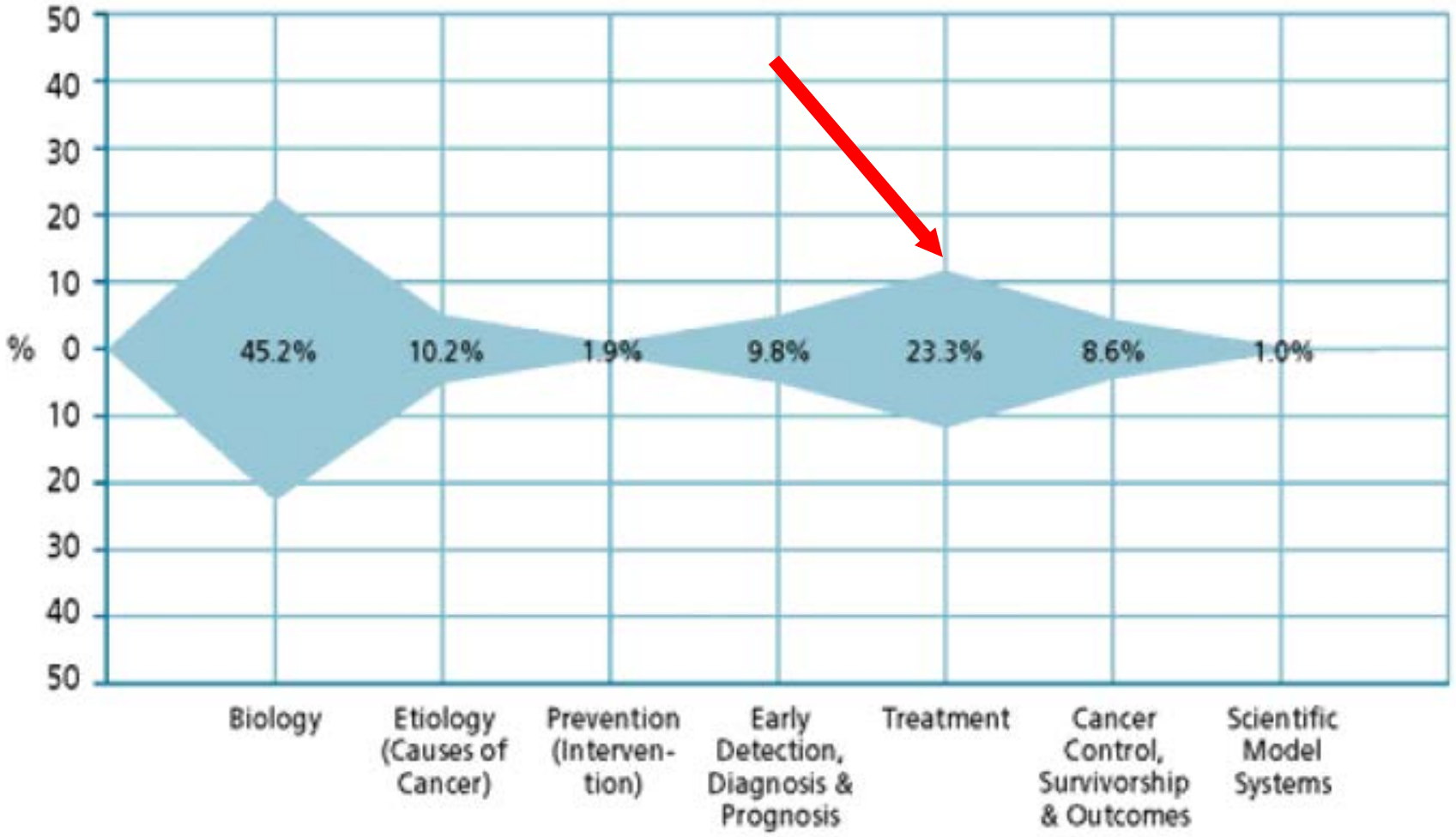

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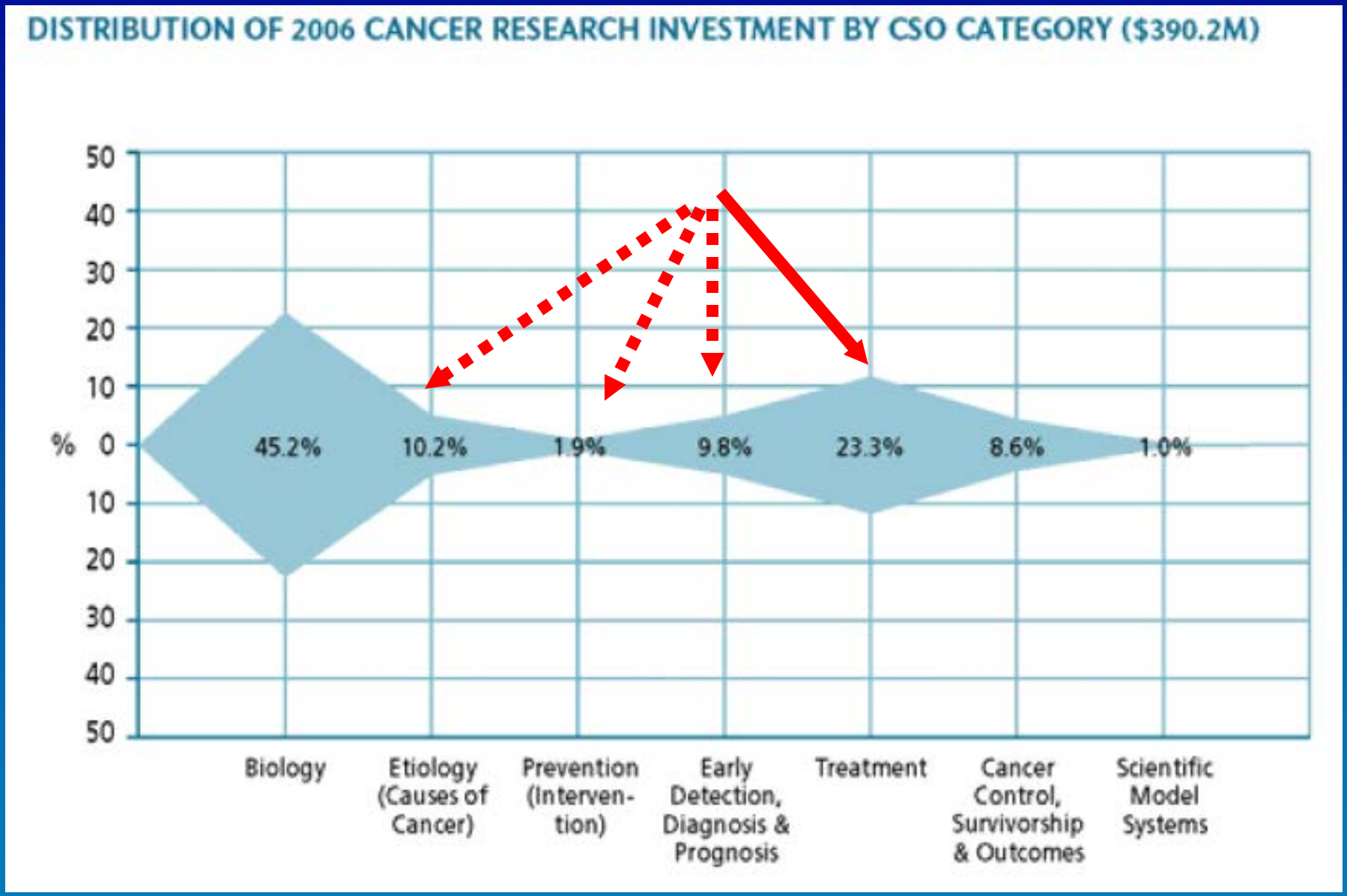

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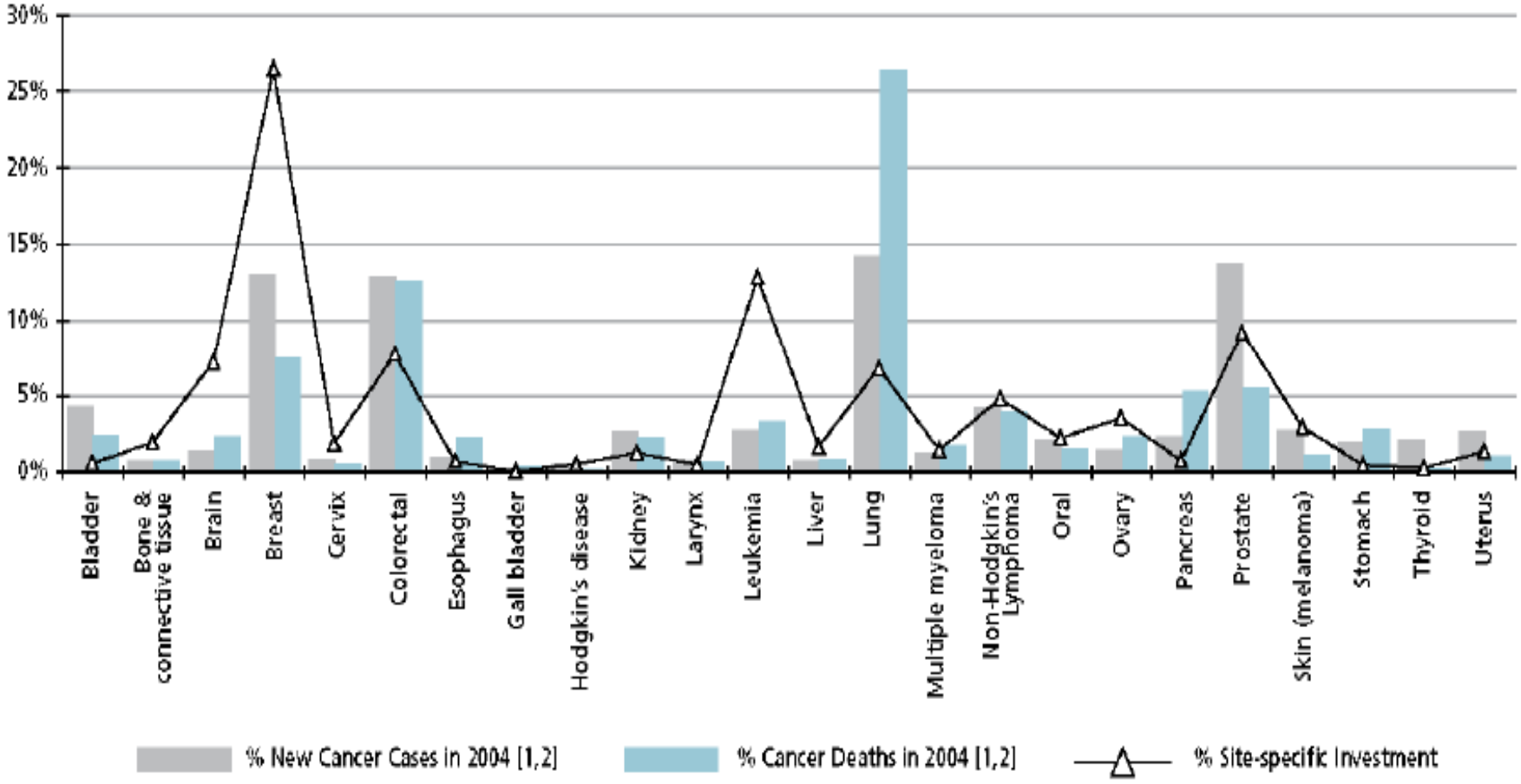
CCRA, 2008: see http://www.ccra-acrc.ca/default_en.htm

DISTRIBUTION OF 2006 SITE-SPECIFIC CANCER RESEARCH INVESTMENT ($183.5M) BY NEW CANCER CASES IN 2004 AND CANCER DEATHS IN 2004



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CCRA, 2008: see http://www.ccra-acrc.ca/default_en.htm

Structure

Structure

NCIC CTG

Can be considered in two major categories:

External

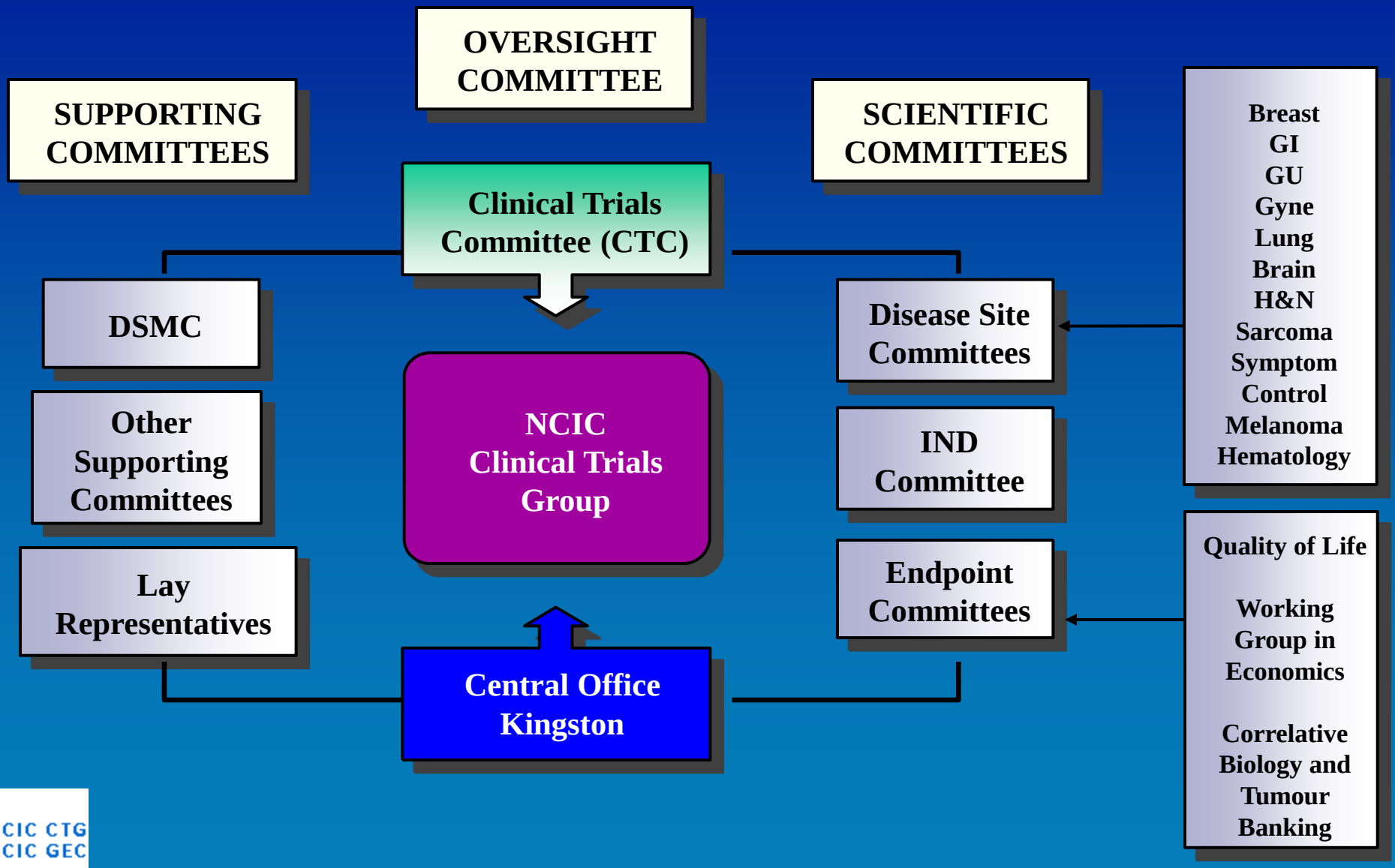
- Network of nearly 100 investigative sites
- Committee structures involving nearly 1000 investigators and other research personnel

Internal

- Head office in Kingston - 150+ staff, 12 faculty

External Organization

External Structure



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External Structure

Refers to network of investigators

- **Canada:** approximately 70 sites
  provincial cancer centers
  university affiliations
  special clinics
- **International:** major cooperative groups
  single sites in many countries

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External Organization

Clinical Trials Committee

- Advisory to the Director
- Considers / advises on policy, roles
- Evaluates all Phase III proposals
- Will assist in evaluating strategic directions
- Has internal + external representation

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External Organization

Data Safety Monitoring Committee

- Advisory to the Director
- Responsible for: safety
  data integrity
  feasibility / relevancy
- Has no internal representation
- Has external + non-CTG representation

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External Organization

Centre Representatives

- Deal with local operations of trial conduct
- Receive correspondence concerning their site

  Agenda, Minutes, Surveys, Drafts
- Communicate information within centre
- Advisory role relationship with central office

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External Organization

Disease Site Committees

- Responsible for scientific leadership
- Each committee has executive and chair
- External and internal representation
- Chair is external, may have international role
- Selection of executive is based on:
  - Scientific leadership
  - Participation
  - Geographic / modality balance

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External Organization

Disease Site Committee Membership

- Each centre has Site Committee members
- Multiple members per centre based disease / therapeutic modalities
- Some Sites have Working Groups
- Members are to *communicate* within their centre, with their executive

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External Organization

Outcome – Based Committees

Correlative Sciences and Tumour Biology

Quality of Life

Working Group on Economic Analysis

- Scientific content to Sites / Trial Committees
- Methodologic research: measurement

  analysis

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External Organization

Other Standing Committees

Radiation Quality Assurance

Audit and Monitoring Committee

Clinical Research Associates

Pharmacy Network

- Role in trial conduct
- Methodologic research

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- **Two programmatic components**

  Investigational New Drugs

  Phase III

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External Structure

Phase III Program

Agenda:

- Led by the Disease Site Committees
- Supported by the Working Groups
- Evaluated / prioritized by the CTC
- Conduct monitored by the DSMC
- Implementation assisted by: CRAs

  Pharmacists

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External Structure

Investigational New Drug Program*

Scope:

- Phase I-II testing of new agents
- Range from '1st in man' to novel combinations
- Prioritized to evaluating targeted mechanisms

Agenda:

- Led by IND executive
- Implemented by IND Committee

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* Elizabeth Eisenhauer and Lesley Seymour

Internal Organization

Internal Structure

Refers to operations at Queen's

Centre for:

- **Methodology and data management**
- **Trial coordination**
- **Quality management:** **assurance**
  monitoring
  safety
  regulatory / ethics
- **Includes 14 faculty and 120 staff**

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Roles of Central Office Staff

Director

- Administer program; formulate, implement policy

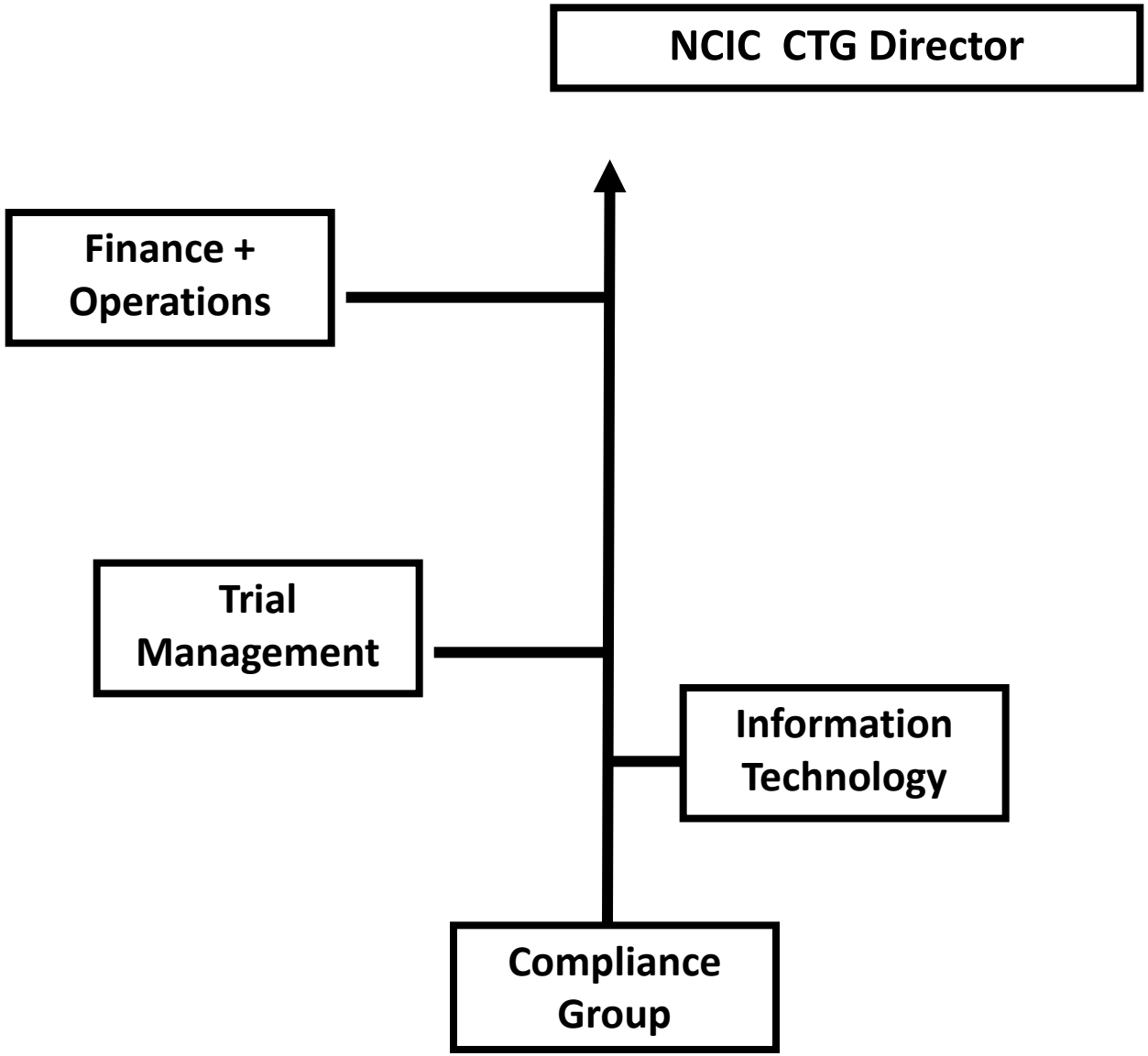
Physician Coordinators (Senior Investigators)

- Provide medical and group input into specific trials, serve as central office medical contacts for each site

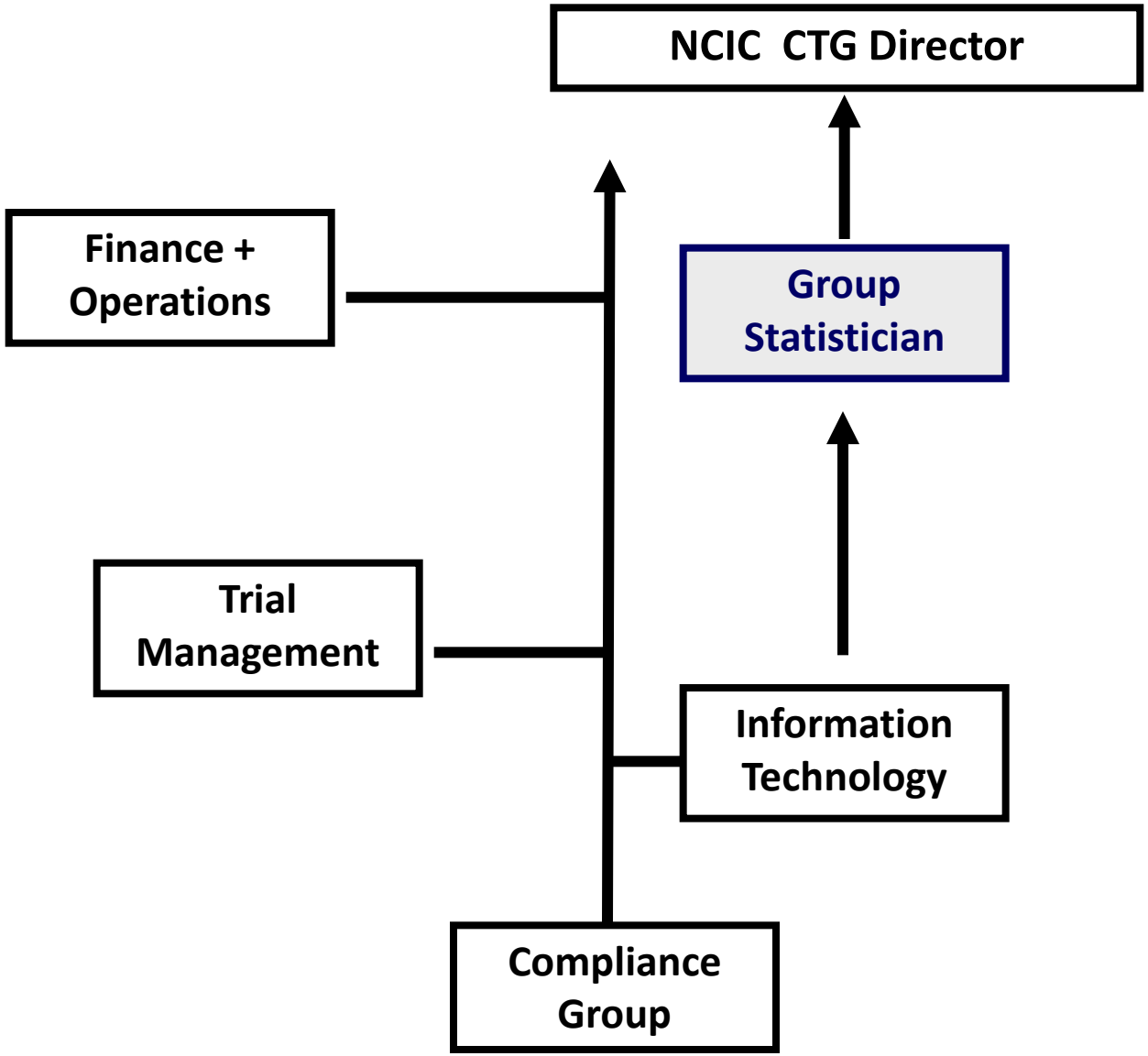
Roles of Central Office Staff

Senior Biostatisticians

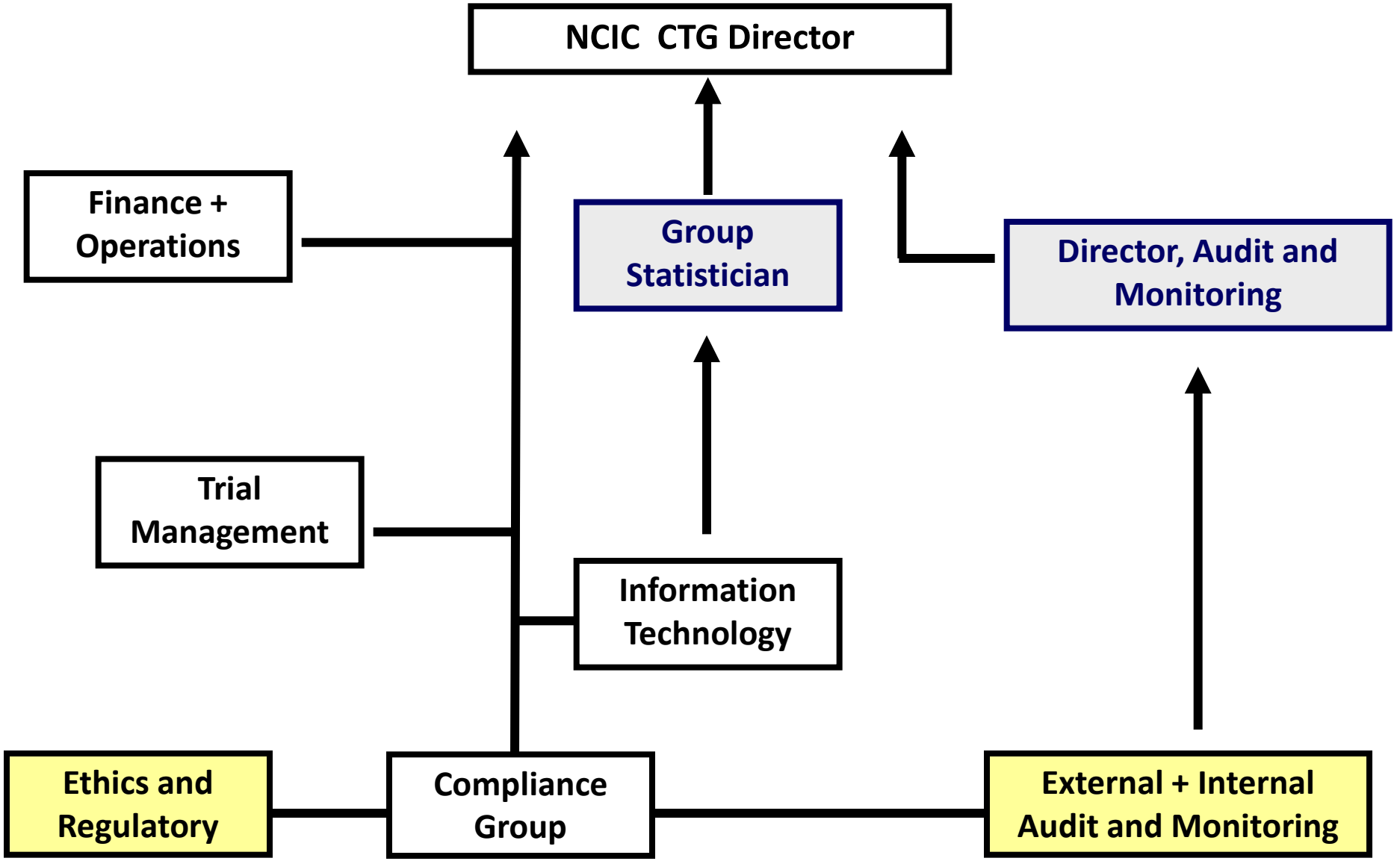
- provide methodologic, statistical input into trials and analyses
- Each is responsible for a slate of sites
- Analyses conducted by biostatisticians, i.e., individuals with BSc or MSc training in statistics plus SAS / Oracle programming skills



NCIC CTG Central Office Organization Chart, 2011



NCIC CTG Central Office Organization Chart, 2011



NCIC CTG Central Office Organization Chart, 2011

Activity Level

External Structure

Phase III Program

Scope:

- Randomized controlled trials
- Selected phase II studies (enablers)

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Broad Accomplishments

1980 – July 2011:

- 437 trials
- 65,000 patients

In 2004-2010 grant cycle:

- 200 trials were in some form of conduct
- 23,000 new patients were accrued

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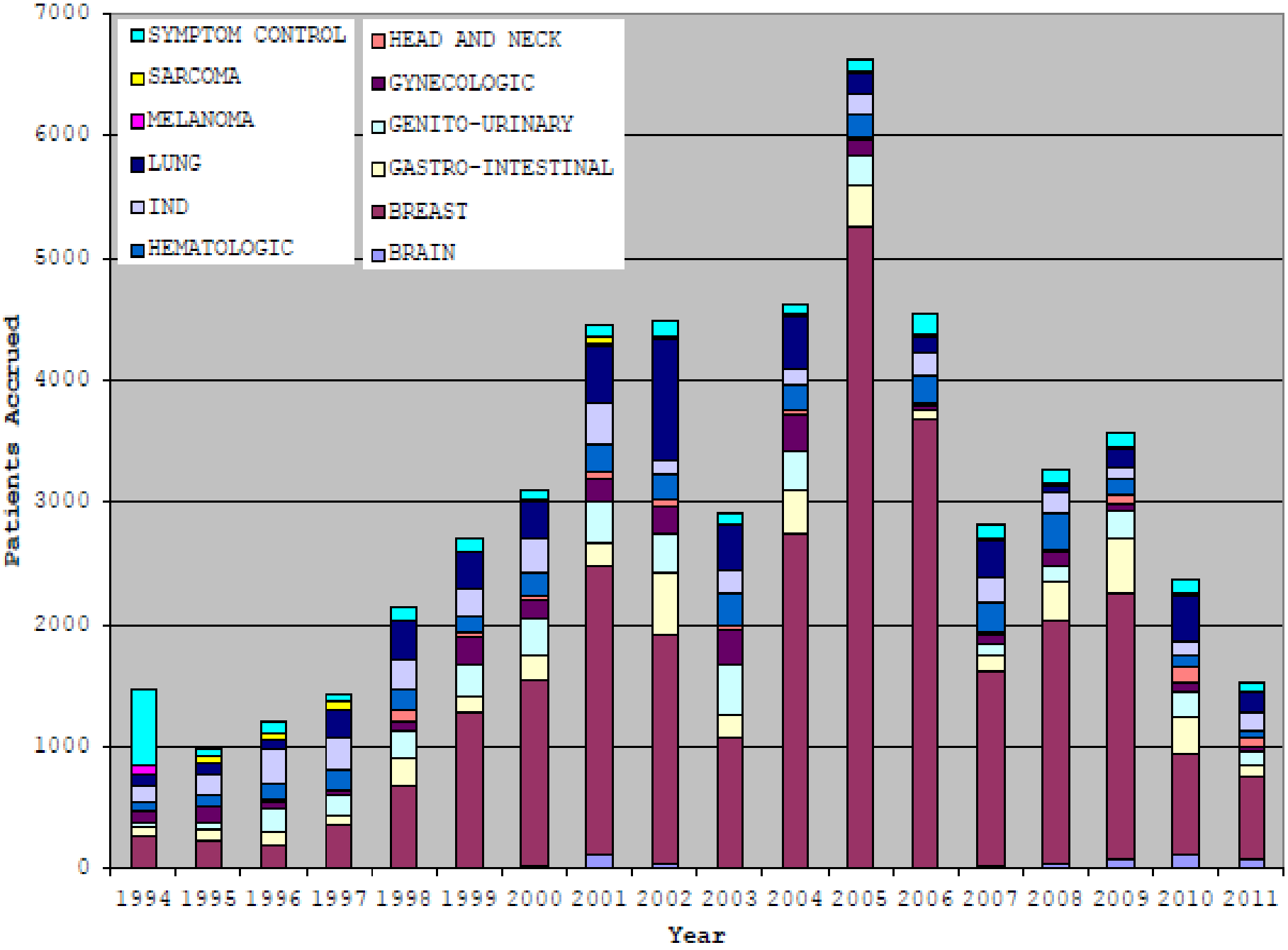
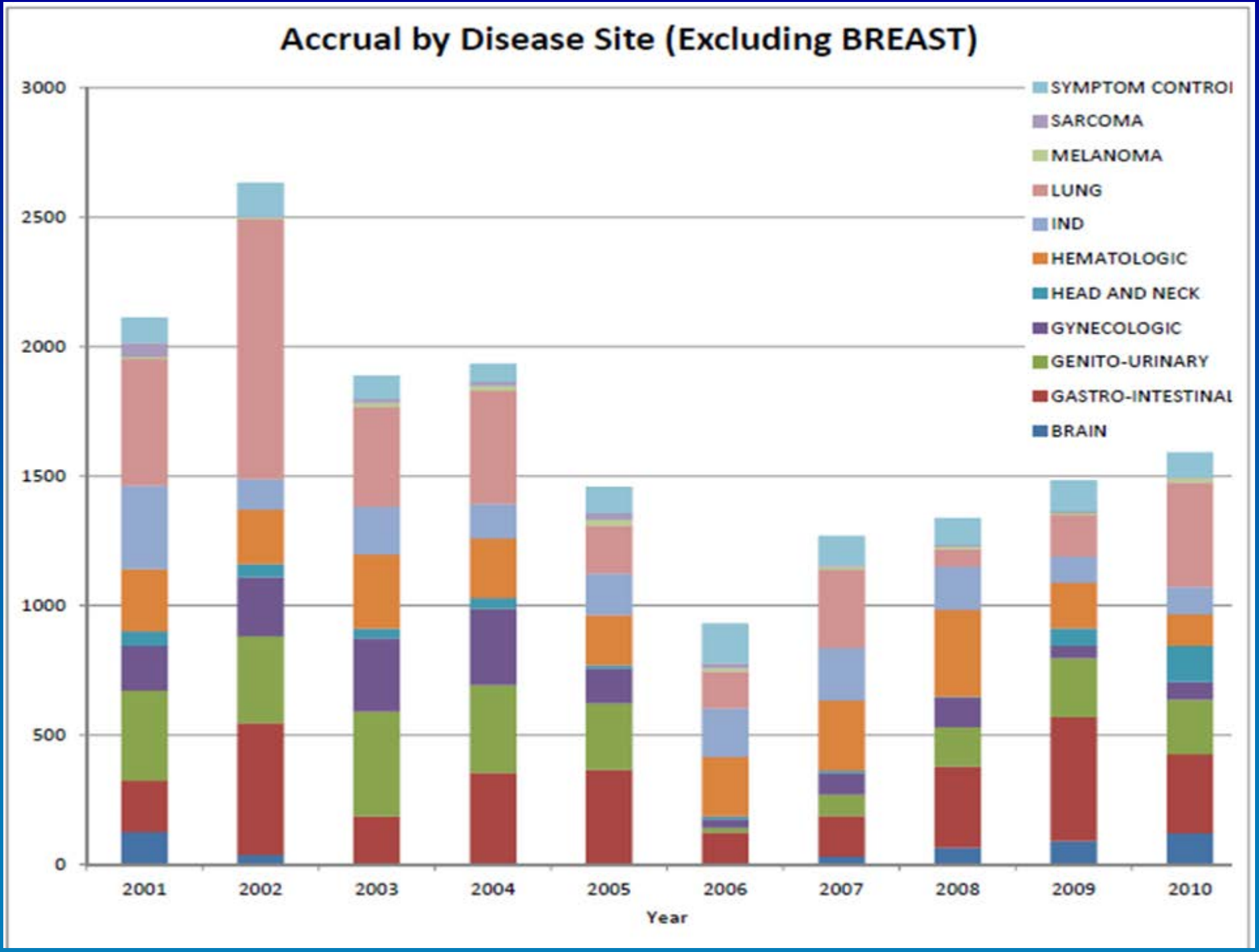
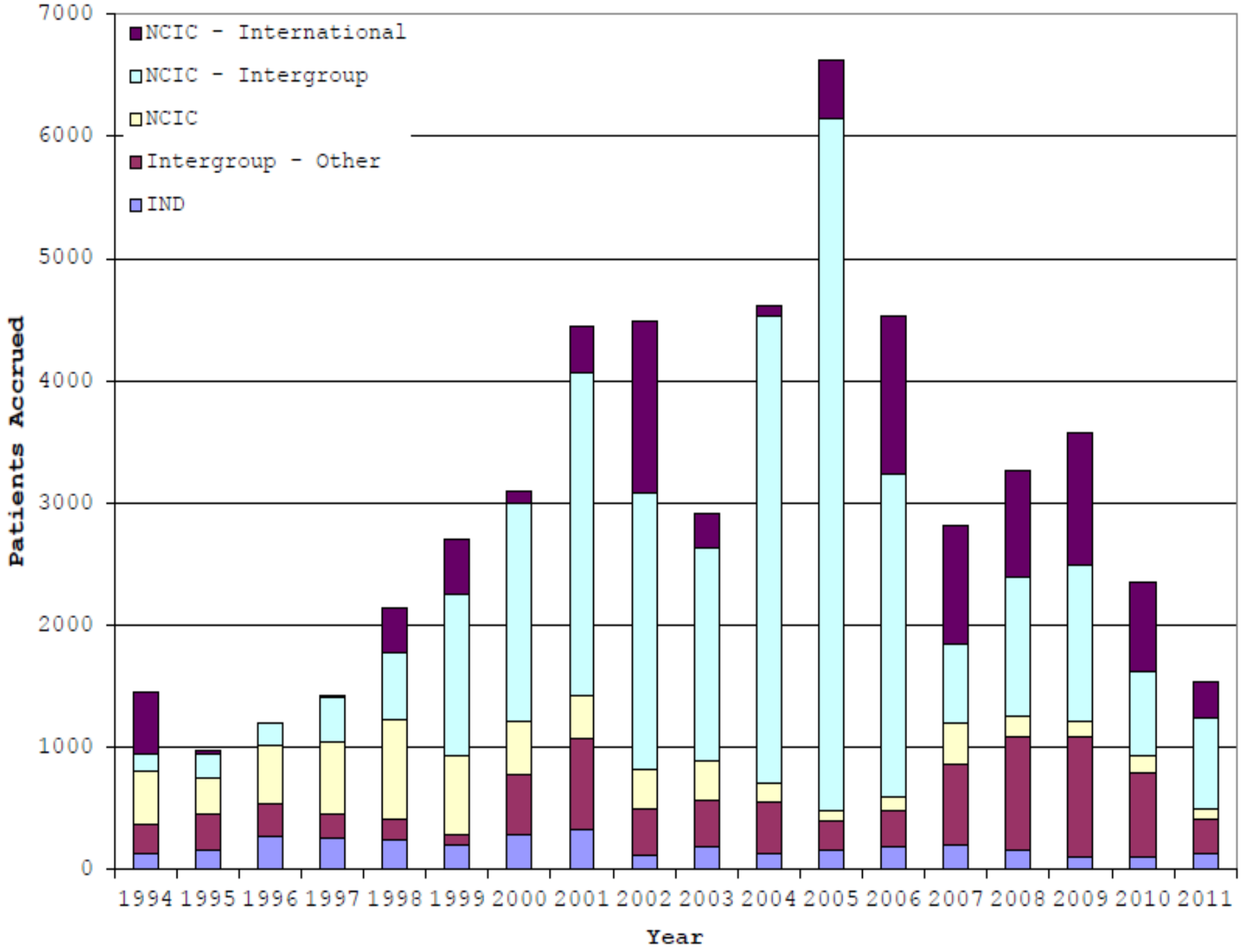

SYMPTOM CONTROL
SARCOMA
MELANOMA
LUNG
IND
HEMATOLOGIC
HEAD AND NECK
GYNECOLOGIC
GENITO-URINARY
GASTRO-INTESTINAL
BREAST
BRAIN
7000
6000
5000
4000
3000
2000
1000
0
Patients Accrued
1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011
Year


Accrual by Disease Site (Excluding BREAST)
3000
2500
2000
1500
1000
500
0
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
Year
SYMPTOM CONTROI
SARCOMA
MELANOMA
LUNG
IND
HEMATOLOGIC
HEAD AND NECK
GYNECOLOGIC
GENITO-URINARY
GASTRO-INTESTINAL
BRAIN

MA32 Accrual by Month as of 2011-AUG-12

Year	Month	Randomizations
2011	AUG	41
2011	JUL	89
2011	JUN	64
2011	MAY	60
2011	APR	53
2011	MAR	51
2011	FEB	50
2011	JAN	49
2010	DEC	33
2010	NOV	25
2010	OCT	27
2010	SEP	9
2010	AUG	2
Total		553


NCIC - International
NCIC - Intergroup
NCIC
Intergroup - Other
IND
Patients Accrued
7000
6000
5000
4000
3000
2000
1000
0
1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011
Year

Selected Deliverables 2004-2010

Publications:

- > 500 trial-related manuscripts and abstracts
- > 110 Central Office faculty research reports
- 18 meta-analyses

"Building Capacity"

- 20 Fellows / PhD / Postdoctoral trainees
- 18 Masters / PhD Theses
- 2 New Investigator Workshops (total N = 70)

Changes to Canadian Health Care Practices

- Aromatase inhibitors for breast cancer (MA.17)
- Adjuvant therapy for lung cancer (BR.10)
- Erlotinib for lung cancer (BR.21)
- Temozolomide for glioblastoma (CE.3)
- Cetuximab for colon cancer (CO.17)
- Chemotherapy for Hodgkin lymphoma (HD.6)
- Limited role of RT in endometrial cancer (EN.5)
- Important role of RT in prostate cancer (PR.3)

Changes to Canadian Health Care Practices

ASCO 2011:

Three Best of ASCO Presentations:

- Aromatase inhibitors prevent breast cancer (MAP.3)
- Regional RT for breast cancer (MA.20)
- Intermittent hormone Rx for prostate cancer (BR.21)

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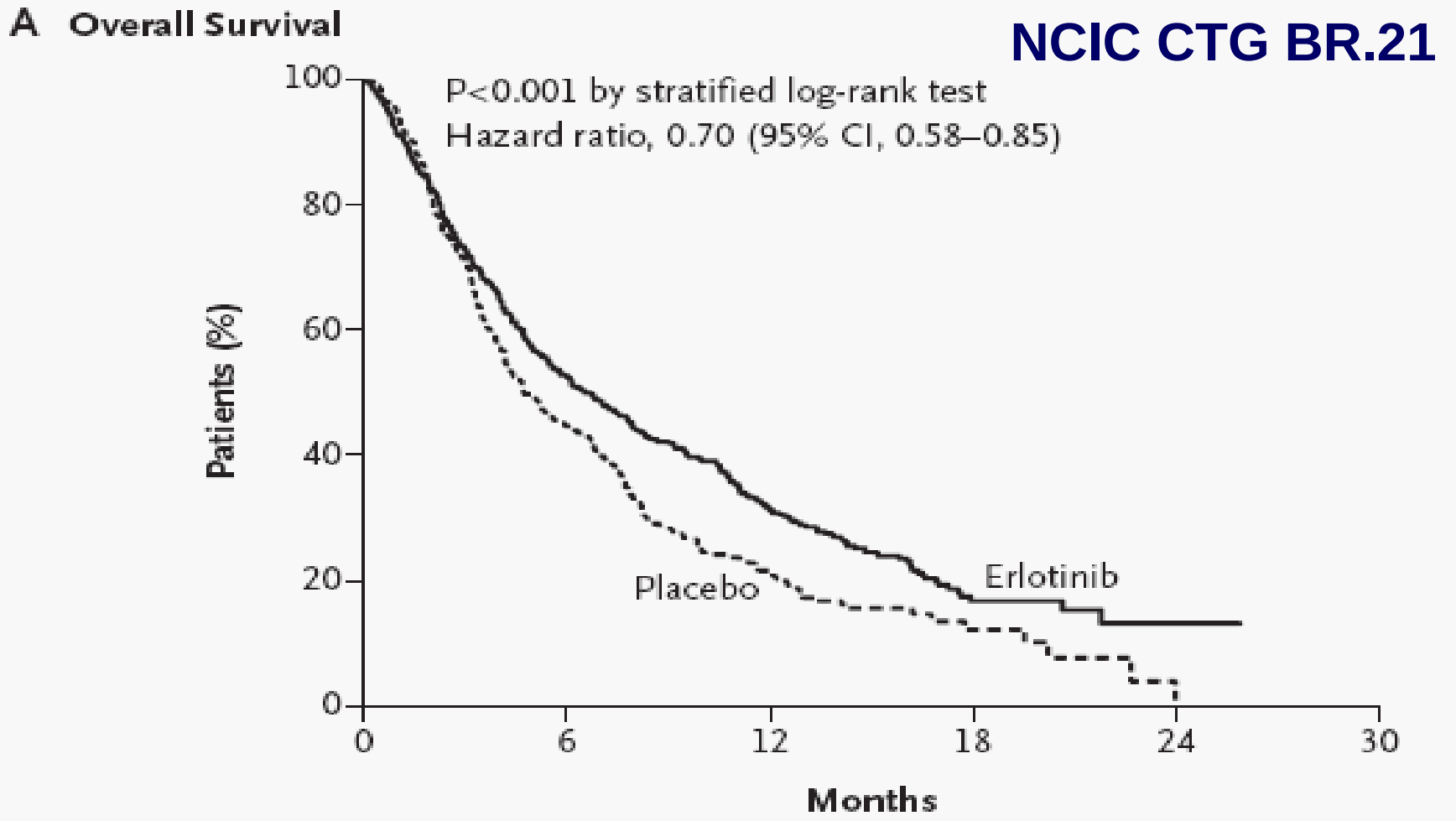
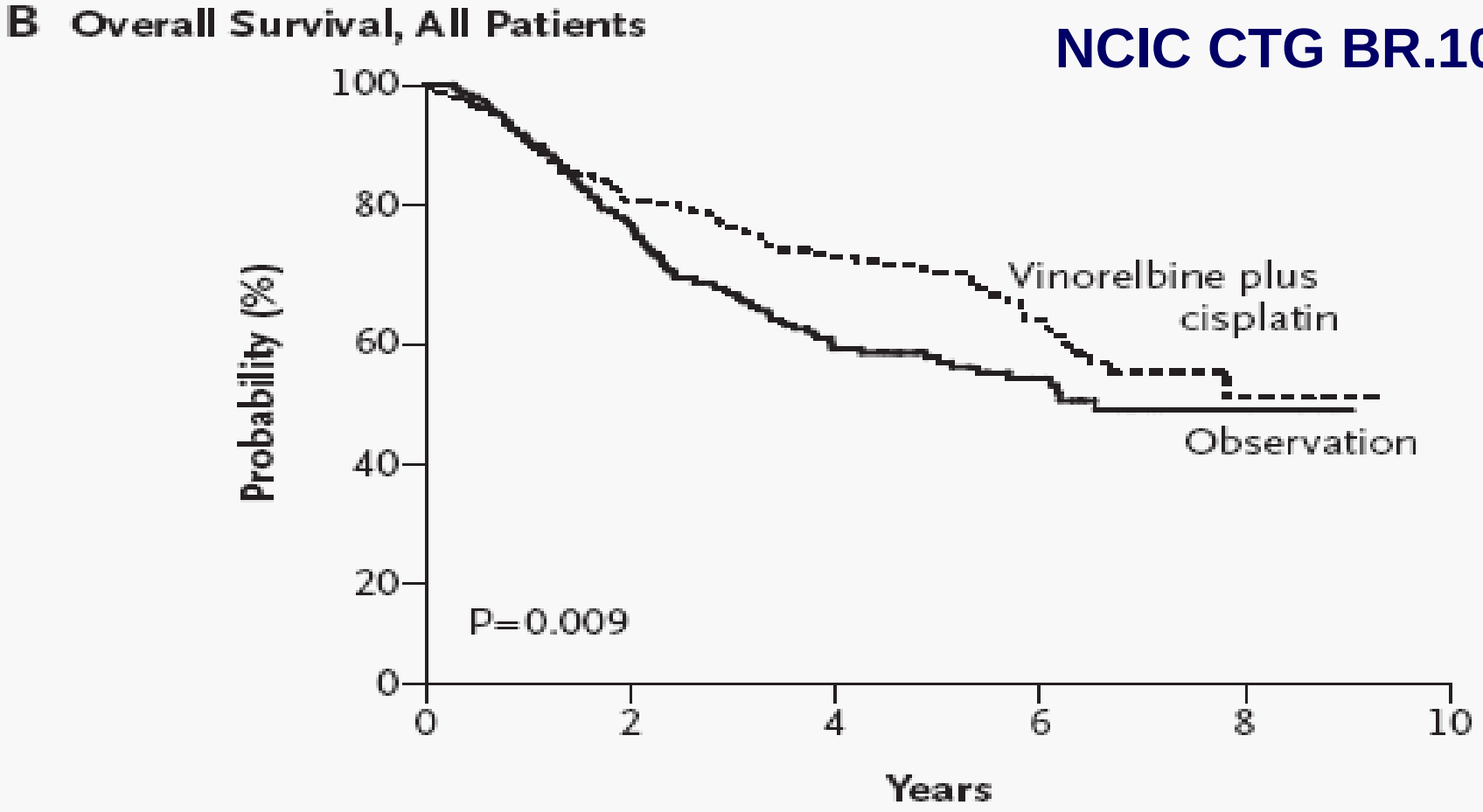
NCIC CTG BR.21

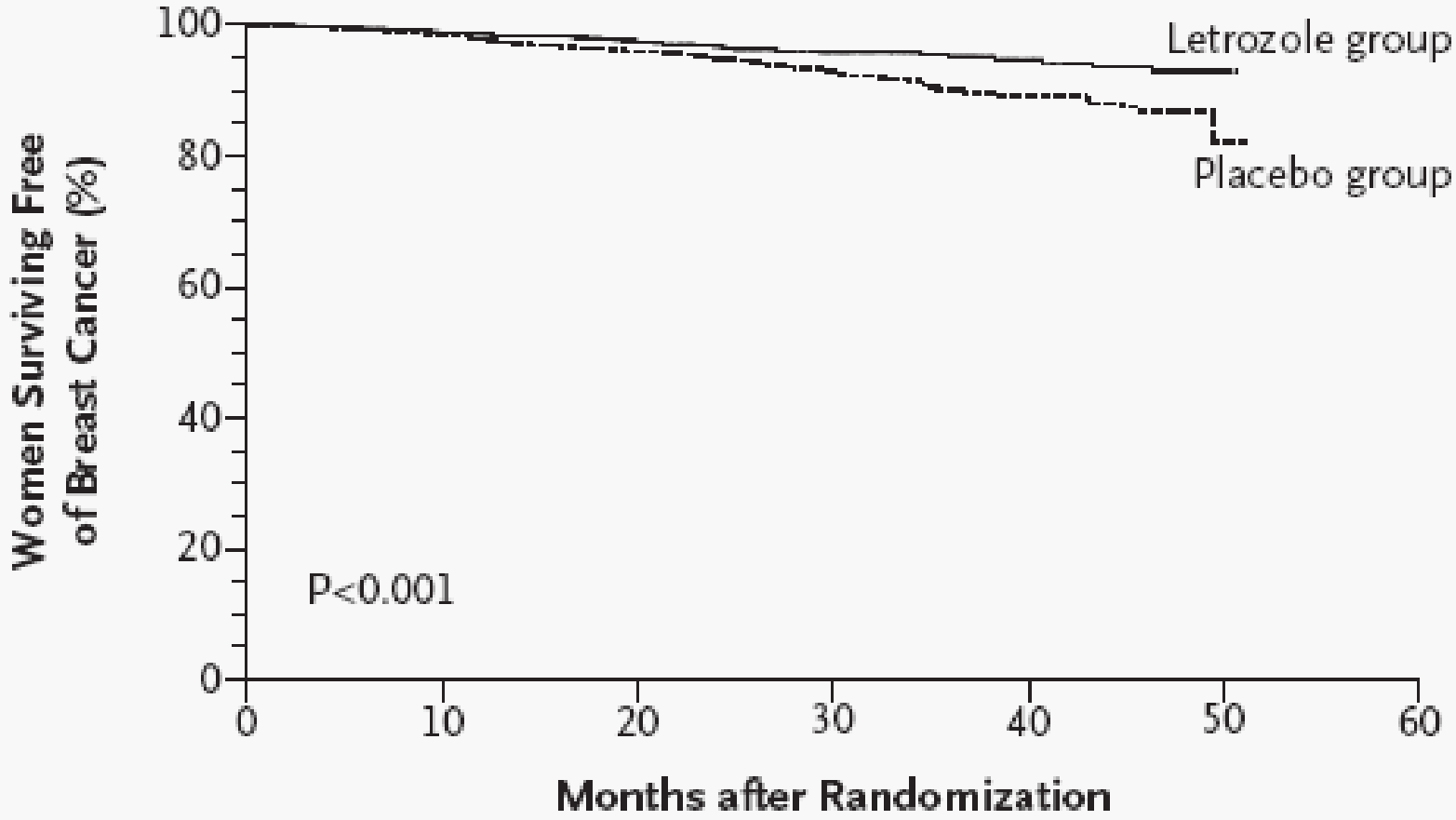


NCIC CTG BR.10



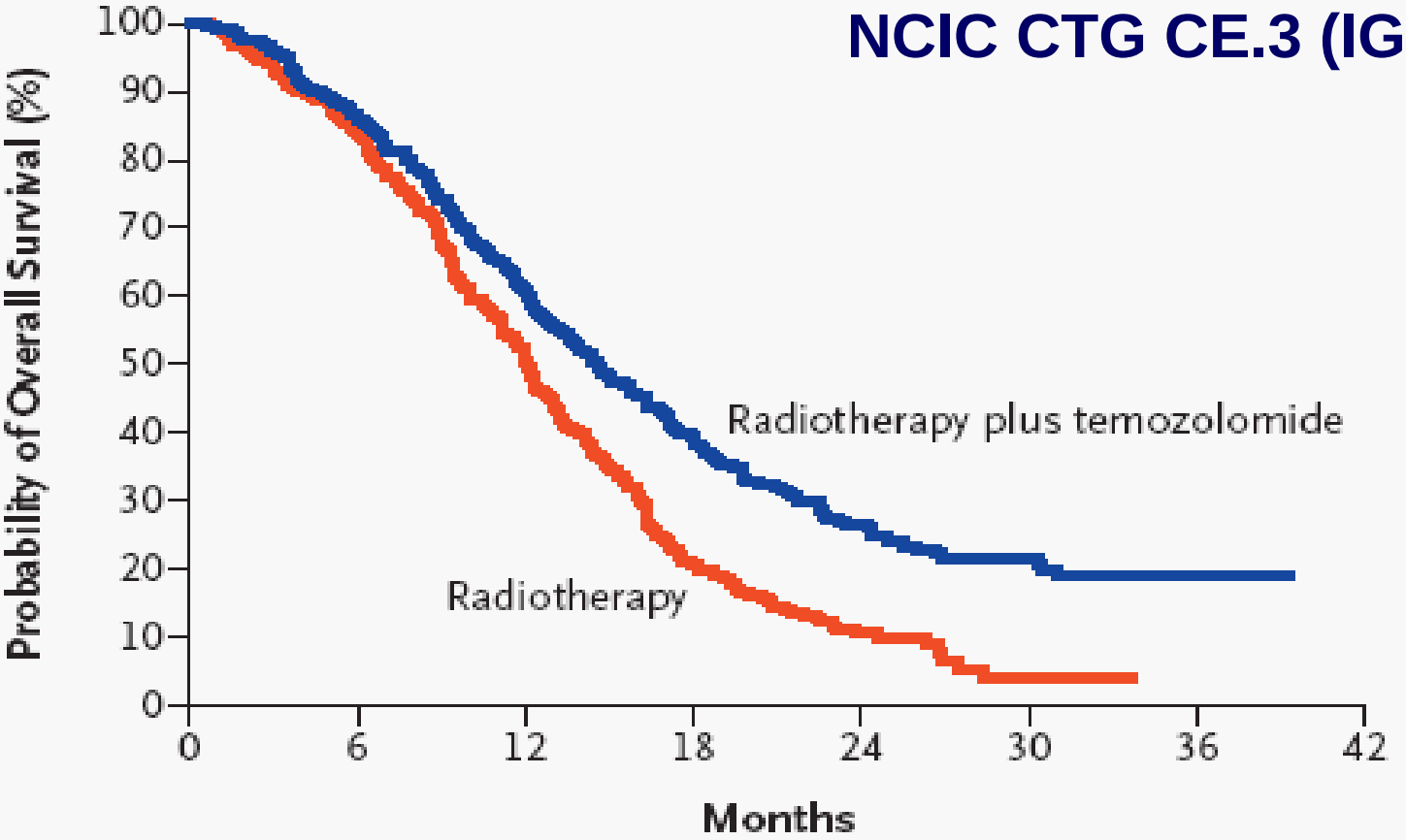
No. at Risk						
Observation	240	182	94	47	13	0
Vinorelbine plus cisplatin	242	193	121	51	10	0

NCIC CTG MA.17



No. at Risk							
Letrozole	2575	2308	1327	624	183	9	0
Placebo	2582	2298	1295	610	180	11	0

NCIC CTG CE.3 (IG)



No. at Risk							
Radiotherapy	286	240	144	59	23	2	0
Radiotherapy plus temozolomide	287	246	174	109	57	27	4

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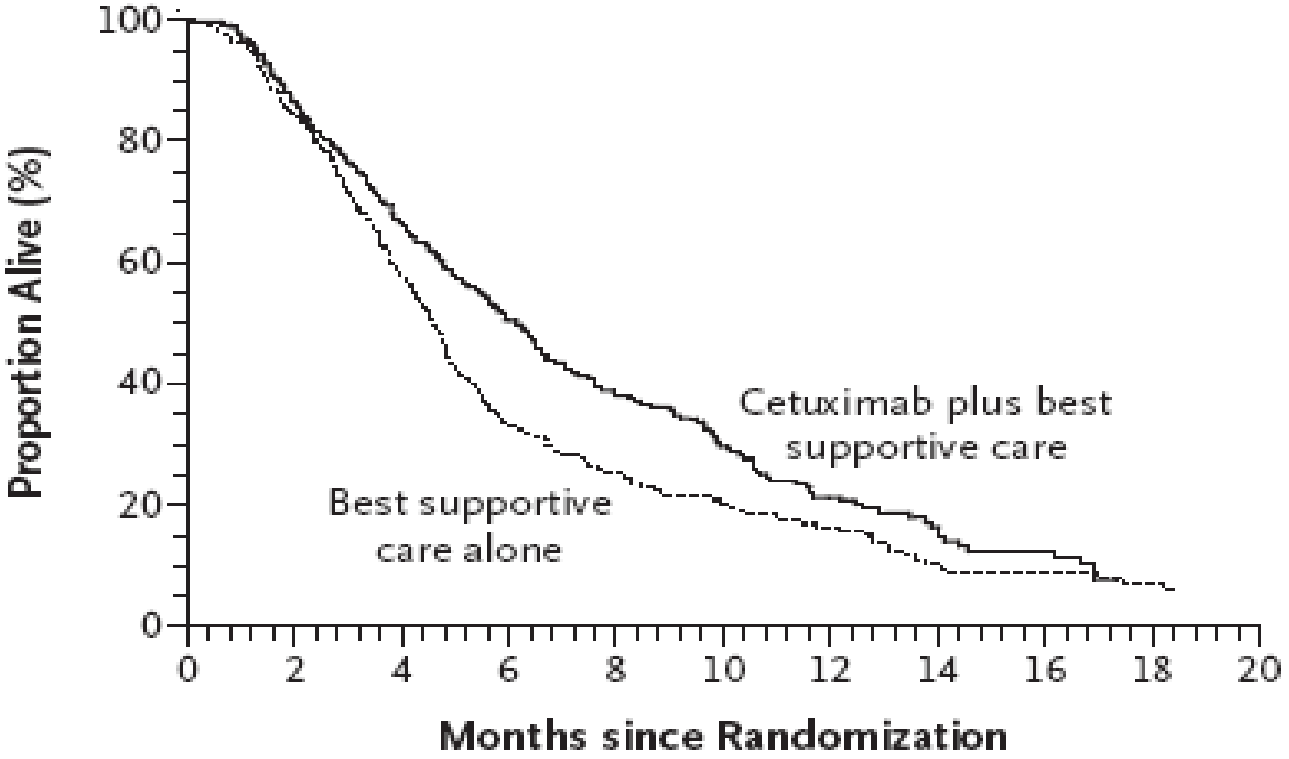
Glioblastoma

Stupp, NEJM 2005

NCIC CTG CO.17

A



No. at Risk											
Cetuximab plus best supportive care	287	245	189	136	87	60	37	20	13	4	1
Best supportive care alone	285	235	157	85	58	37	26	15	11	8	4

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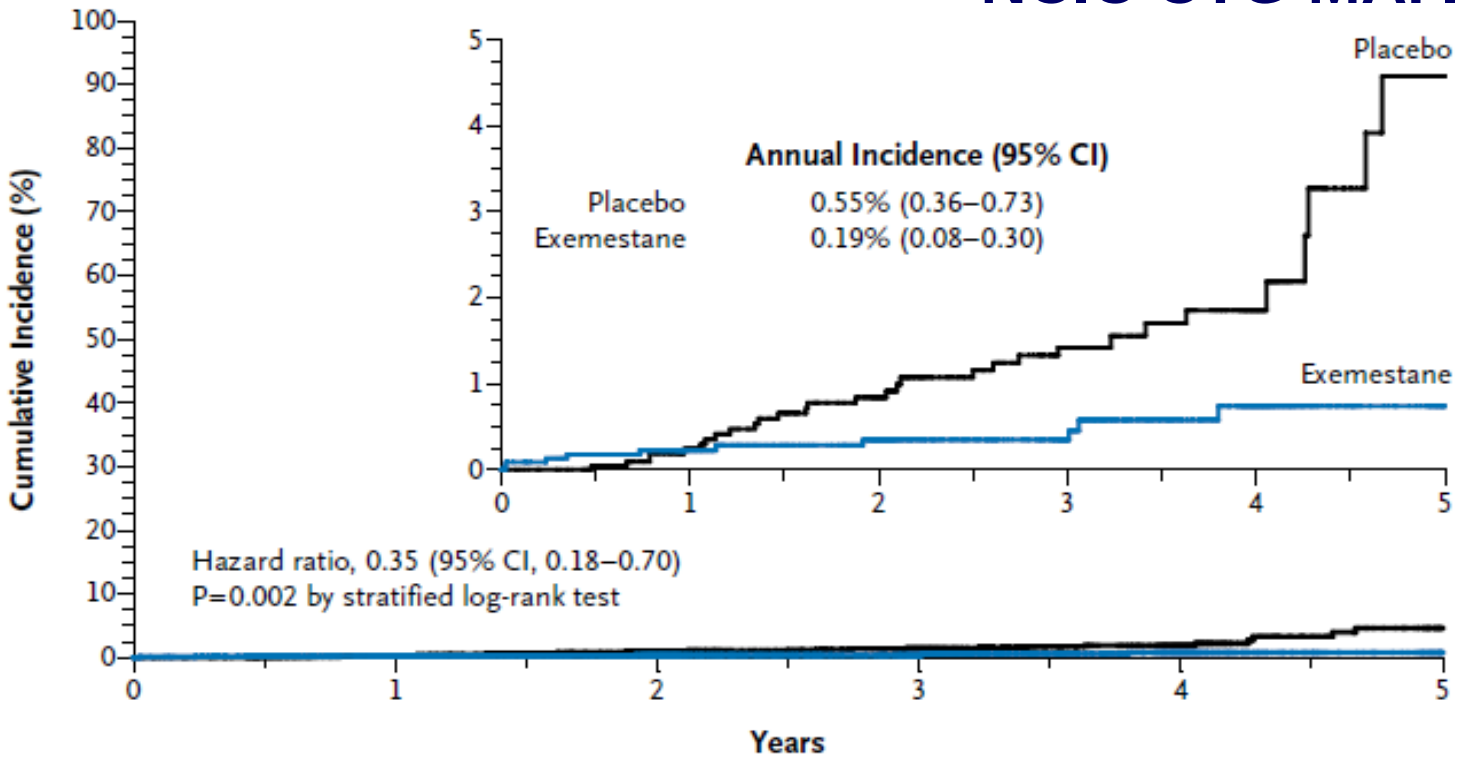
Colon Cancer

Jonker, NEJM 2007

NCIC CTG MAP.3



No. at Risk

Placebo	2275	1905	1468	986	477	82
Exemestane	2285	1902	1468	980	464	77

Figure 1. Cumulative Incidence of Invasive Breast Cancer.

CI denotes confidence interval.

NCIC CTG: Productivity

IND Program

- More than 190 trials
- Enrolment of ~ 4,400 patients
- Testing of more than 70 new agents
- Multiple examples of:

  ‘to phase III’ results

  successful correlative observations

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IND Program: Goals

- Acquire new agents for study in Canada
- Generate results leading to phase III trials
- Advance Phase I-II trial methodology
- Include laboratory / imaging correlative studies
- Train new specialists in drug development

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Acquire Novel Agents for Study

High priority agents

- Novel / target - specific cytostatics / cytotoxics
- Antimetastatic agents or angiogenesis inhibitors
- Cytoprotectors or modulating agents
- Hormones / biologicals with immune basis

2008 – 2009 Strategic Planning Process

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

2008-09 Strategic Planning Process

Background:

- Completion of US NCI/CTEP review
- Entering a CCSRI grant cycle
- Important environment changes:

  Opportunities

  Threats

Framing the Issue

How do we develop a high-quality strategic agenda, and how do we operationalize this through our Central Office and at our member centres?

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Process

1. Central Office Background
2. 2008 Fall Meeting Retreat

Scientific Strategy **Operational Issues**

Systematic subsequent steps

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Some Specific Recommendations

Group-Wide Strategic Agenda

Within the Phase III Program:

a) priority should be given to trials that directly change health care delivery practices and/or that address a paradigm-changing treatment principle;

b) priority should be given to trials that include endpoints that address multiple outcome domains including effectiveness, quality of life, economic implications, and correlative / translational research that includes biomarker development; and,

c) in meeting the priorities stated in a) and b) above, the need to conduct trials with international partners should be expected.

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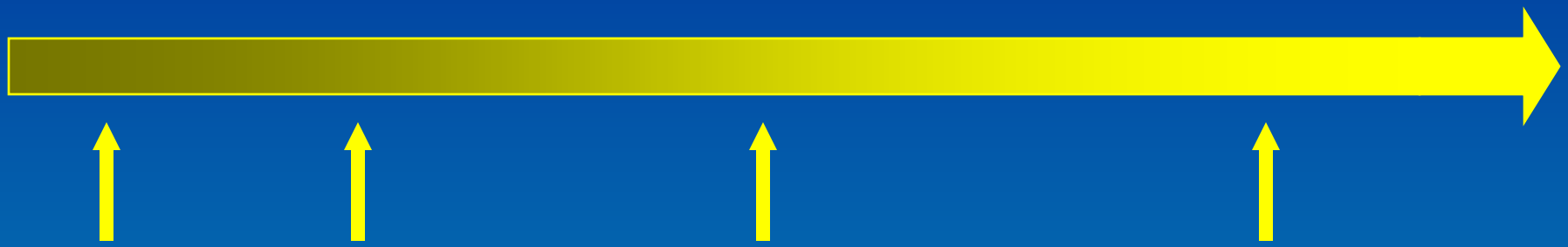
Recommendation #3

Progression of Trials



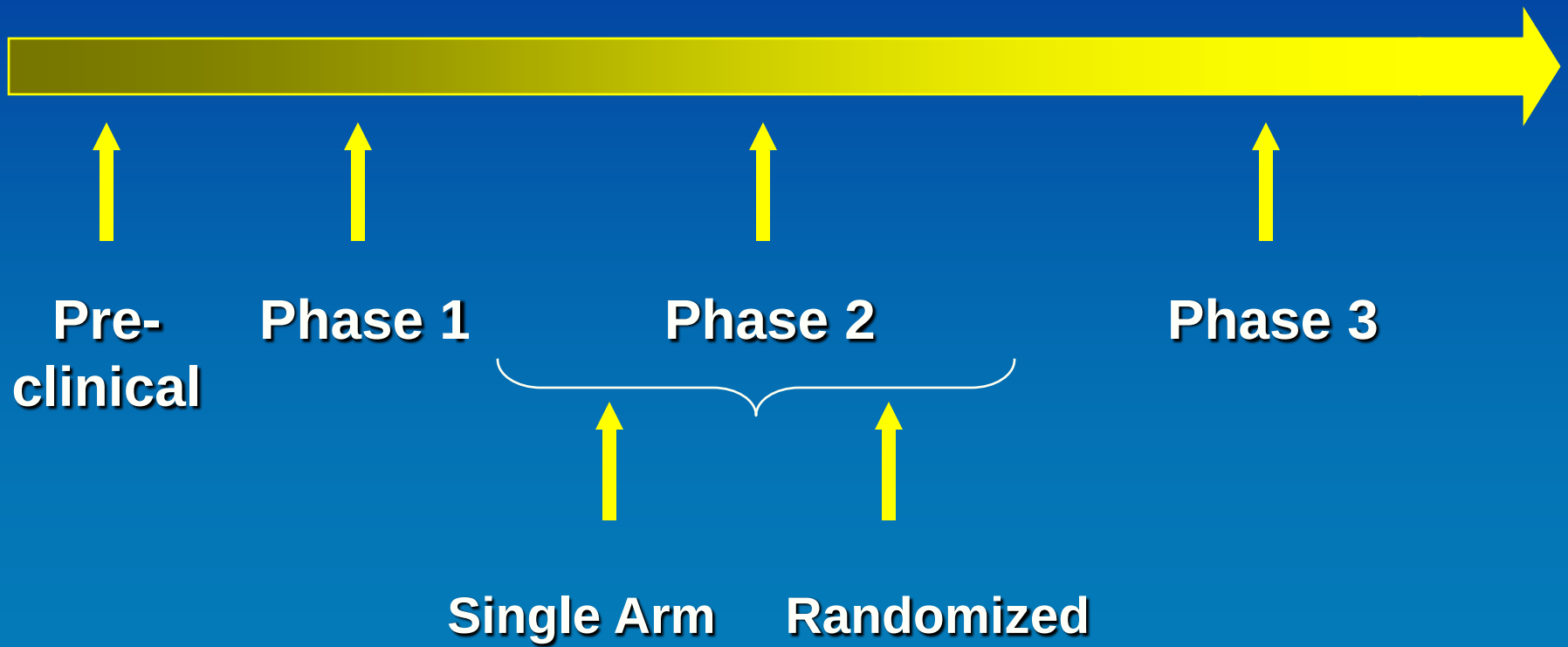
Pre-clinical

Phase 1

Phase 2

Phase 3

Progression of Trials



NCIC CTG
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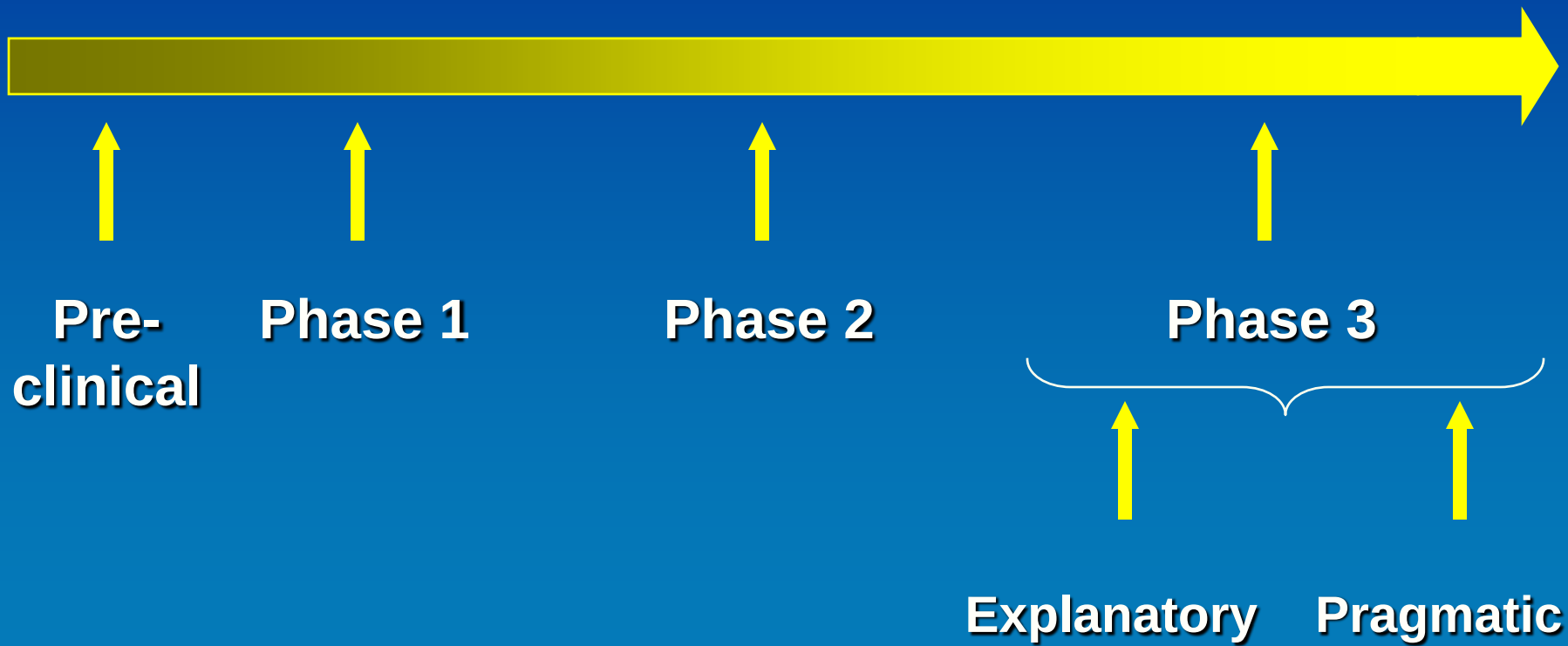
Progression of Trials



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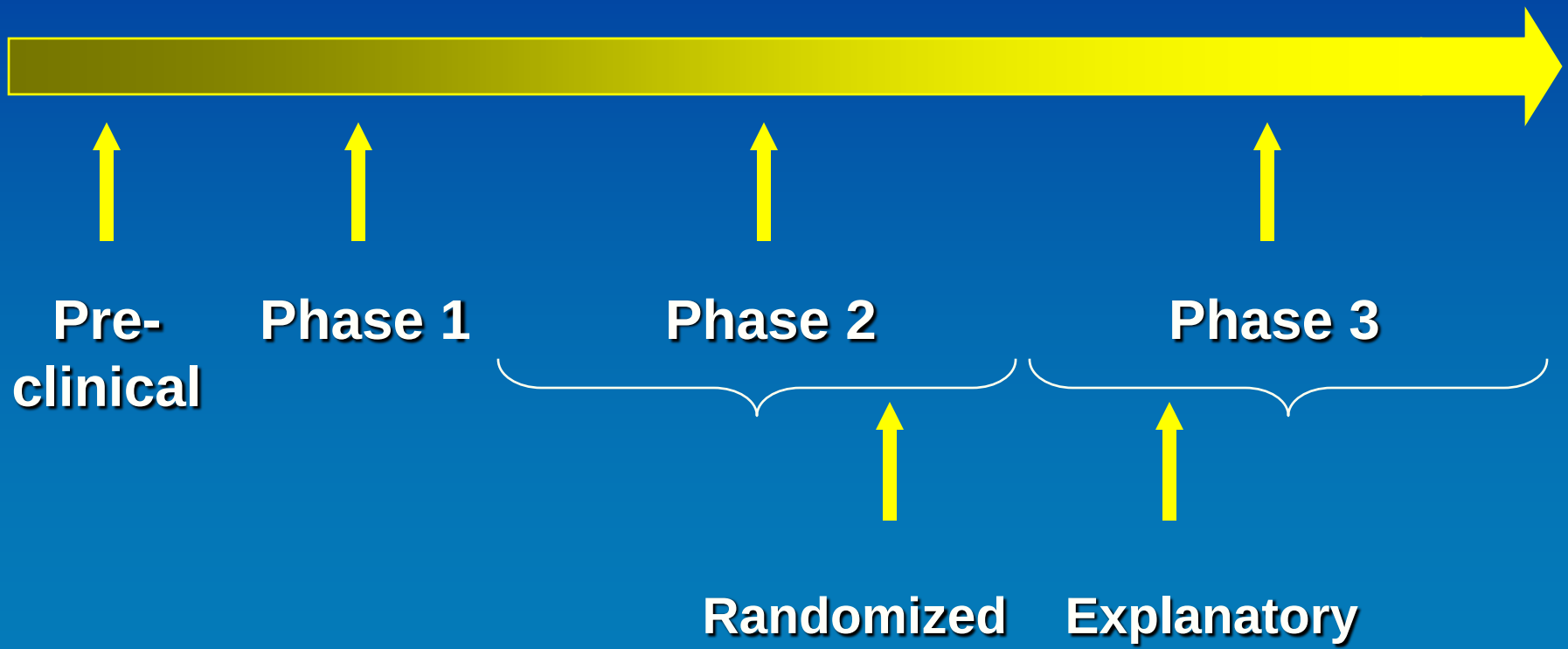
Progression of Trials



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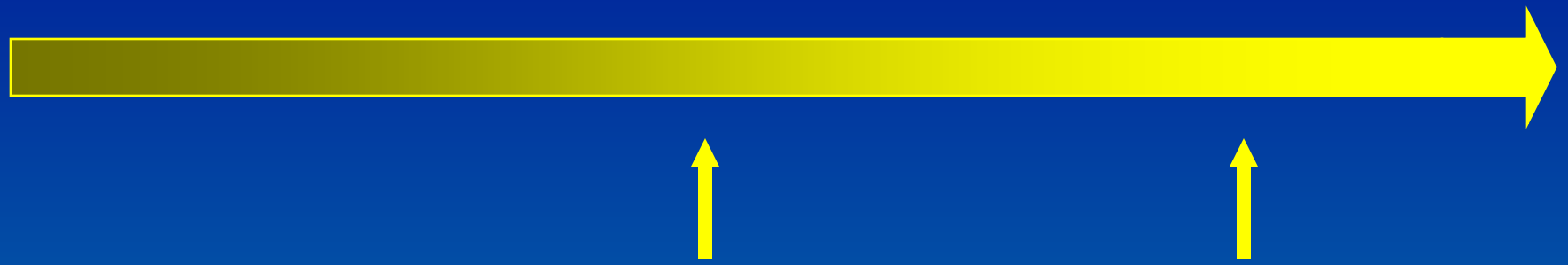
Progression of Trials: Phase 3



	EARLY	LATE
Patients	Metastatic	Adjuvant
Design Principles	Explanatory	Pragmatic
Regulatory Approval	Primary	Secondary
Data Collection	Detailed	Less Detailed (?)

Progression of Trials: Phase 3

EARLY

Emphasis of biologic POP

Lesser direct relevance to health care delivery

Correlative biology may emphasize tumour factors

LATE

Progression of Trials: Phase 3

EARLY	LATE
Emphasis of biologic POP	Emphasis of effectiveness
Lesser direct relevance to health care delivery	Direct relevance to health care delivery is essential
Correlative biology may emphasize tumour factors	Correlative biology may emphasize patient factors

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Some NCIC CTG Trials: Explanatory vs. Pragmatic (1)

TRIAL	SS	HR	P	Absolute Difference*
PA.3	569	.82	.038	11 days (6.24 vs. 5.9 mos)
BR.21	731	.73	.001	60 days (6.7 vs. 4.7 mos)
CO.17	572	.68	<.001	45 days (6.1 vs. 4.6 mos)

* Median overall survival

Some NCIC CTG Trials: Explanatory vs. Pragmatic (2)

TRIAL	SS	HR	P	Absolute Difference
PA.3	569	.82	.038	11 days (6.24 vs. 5.9 mos)
BR.21	731	.73	.001	60 days (6.7 vs. 4.7 mos)
CO.17	572	.68	<.001	45 days (6.1 vs. 4.6 mos)

- Two trials were published in NEJM
- The 3rd was an ASCO plenary paper
- All 3 had important correlative studies
  - Two of these were NEJM publications

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Progression of Trials: Phase 3

EARLY

Emphasis of biologic POP

Lesser direct relevance to health care delivery

Correlative biology may emphasize tumour factors

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Progression of Trials: Phase 3

EARLY

Emphasis of biologic POP

Lesser direct relevance to health care delivery

Correlative biology may emphasize tumour factors

Nature of the paradigm change

Quality of the CSTB

Progression of Trials: Phase 3

LATE

Emphasis of effectiveness

Direct relevance to health care delivery is essential

Correlative biology may emphasize patient factors

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Progression of Trials: Phase 3

Magnitude of impact to health care delivery

LATE

Emphasis of effectiveness

Direct relevance to health care delivery is essential

Correlative biology may emphasize patient factors

The Nature of Collaborations

The NCIC CTG should prioritize phase III trials that involve international collaborations. Among these collaborations, those associated with formal structures and processes (e.g., the NCI/CTEP Steering Committee / Task Force initiative) should be given the greatest priority. There is a need to more clearly enunciate the principles to be used to prioritize development of potential collaborations with other international partners.

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Recommendation #7

Correlative / Translational Research

The NCIC CTG should prioritize phase III trials that include high-quality translational research. Given the unique role of phase III trials in the process of biomarker development, trials that include biomarkers as integral components of trial design should be particularly prioritized.

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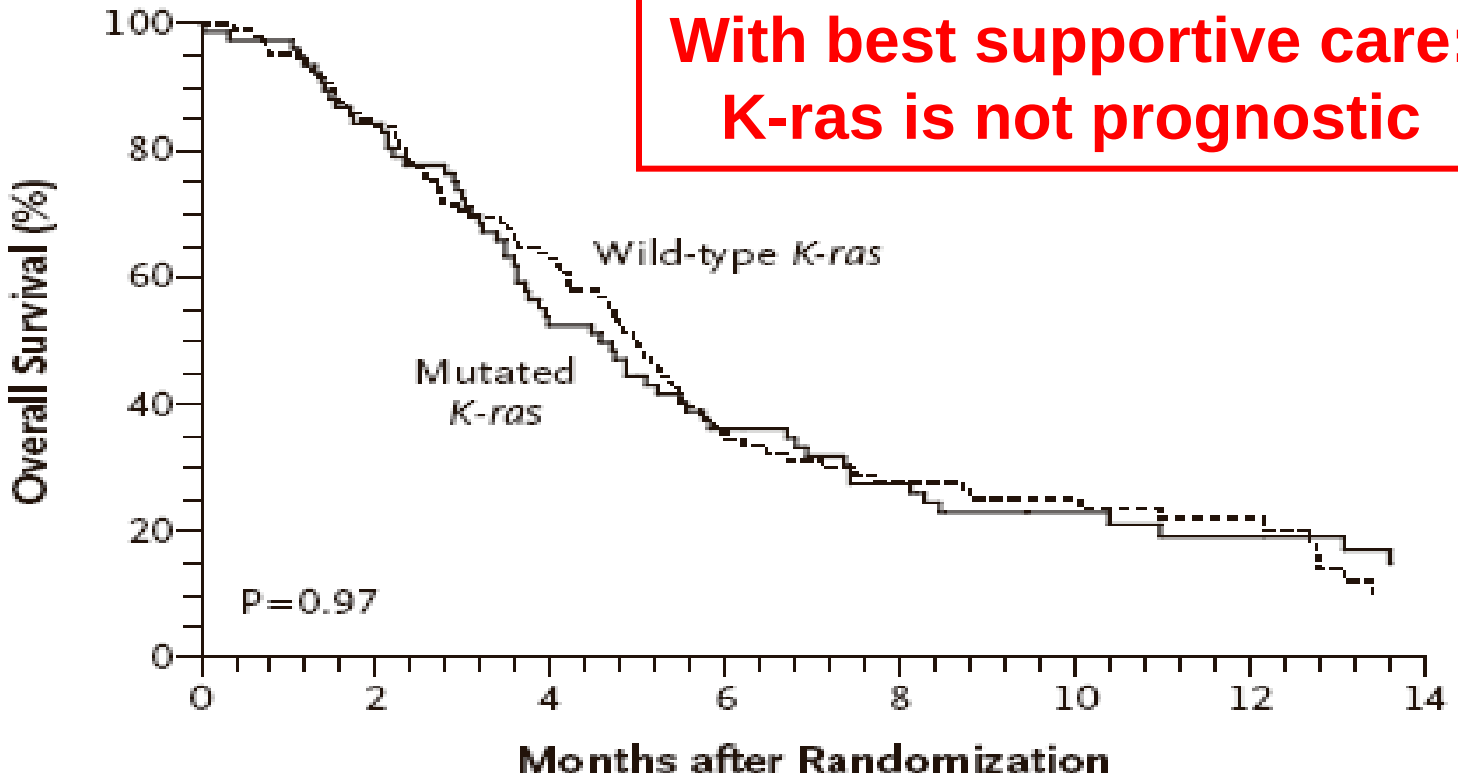
Recommendation #11

With best supportive care: K-ras is not prognostic



No. at Risk

Mutated *K-ras*	76	64	39	26	19	12	10	7
Wild-type *K-ras*	105	88	65	34	23	17	12	5

Figure 3. Kaplan–Meier Curves for Overall Survival According to *K-ras*–Mutation Status among Patients Receiving Supportive Care Alone.

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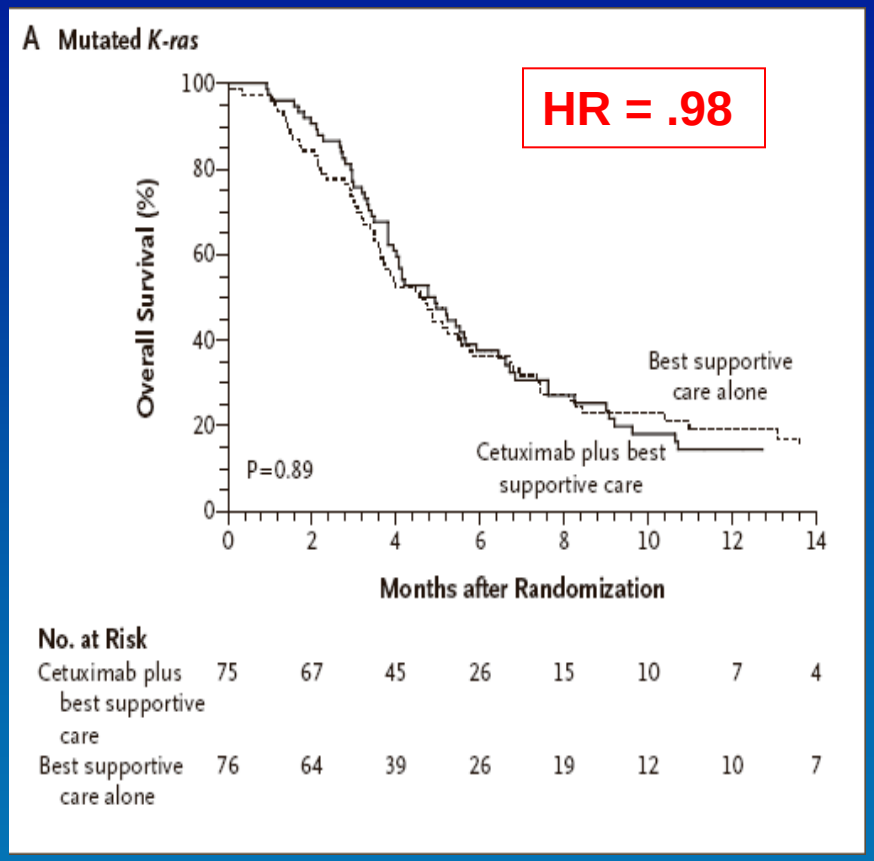
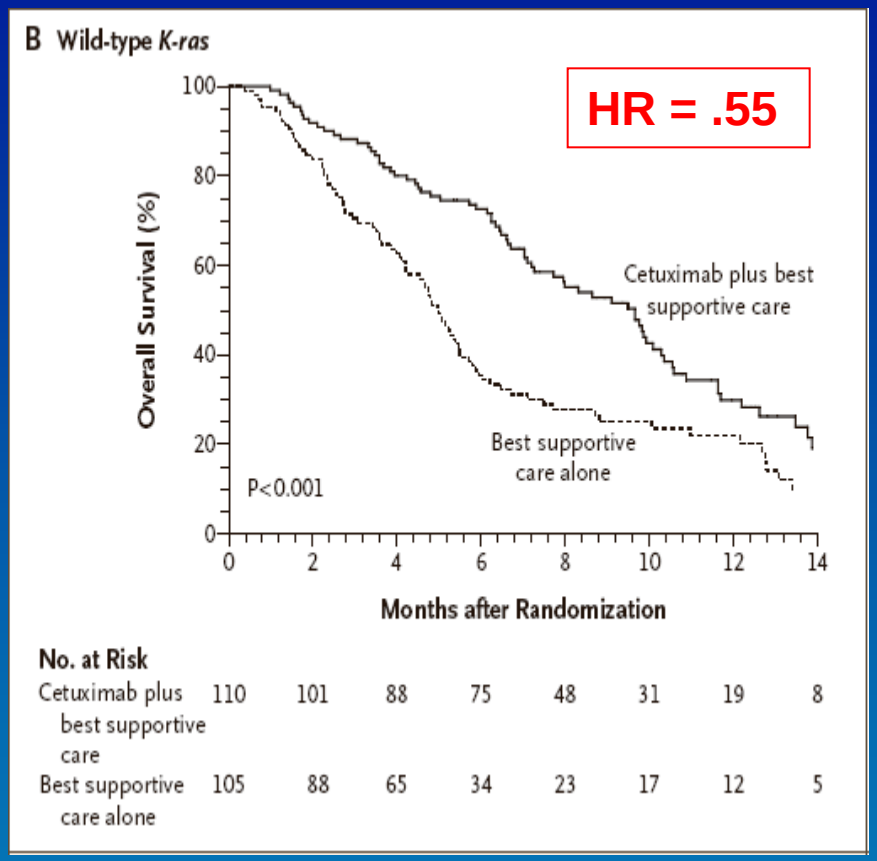
Karapetis, NEJM 2008

Overall Survival: By K-ras Mutational Status





Test for interaction P < 0.001

K-ras is a predictive marker

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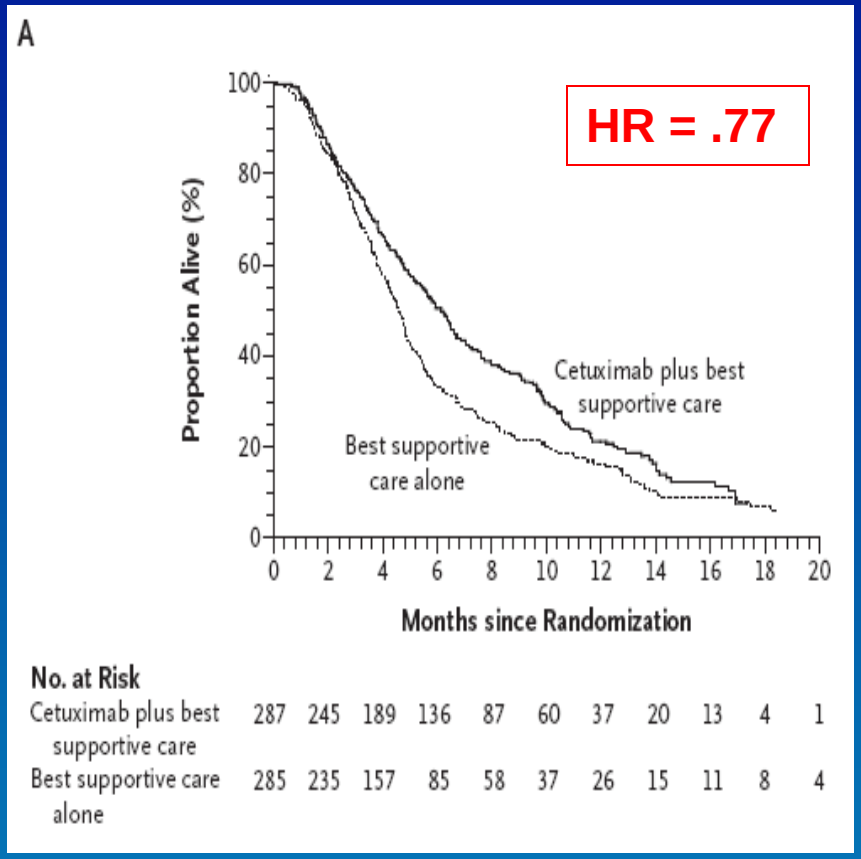
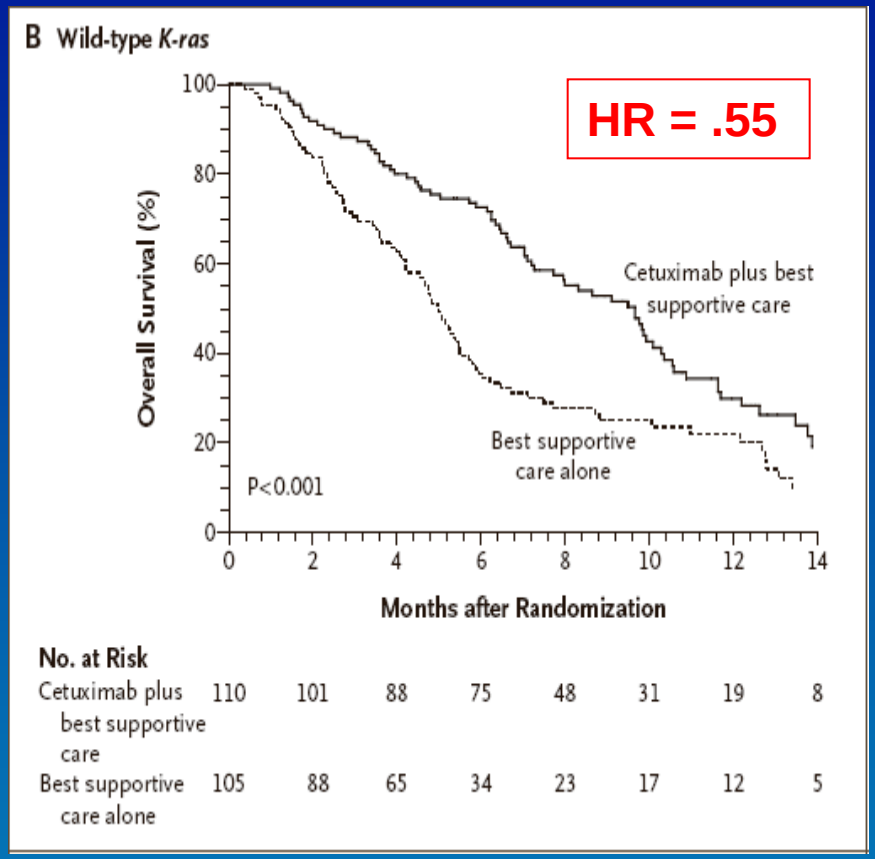
Karapetis, NEJM 2008

Economic Evaluation: Implications of K-ras Determination





All Patients:

CEA ratio: $199,742 / LYG

CUA ratio: $299,613 / QALY

K-ras Wild-type Patients:

CEA ratio: $120,061 / LYG

CUA ratio: $186,761 / QALY

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Mittmann JNCI, 2009

Specific Categories

1. To assess ***novel therapeutics***, including evaluation of new systemic agents, in phase I-III clinical trials.

2. To conduct ***pragmatic phase III trials***. The NCIC CTG recognizes the unique positioning of an academic cooperative group in being able to conduct these trials that compare or test interventions for the purpose of direct application to health care delivery policies. This role is particularly important in informing delivery of health care that is relevant to Canadians.

Specific Categories

3. To evaluate ***biological endpoints*** within clinical trials; in particular, identifying biomarkers that facilitate individualization of therapies may be crucial to improving the outcomes of cancer patients.

4. To evaluate ***interventions that will prevent cancer***. Cancer prevention can be considered as primary (interventions in patients who do not have cancer), secondary (screening) or tertiary (prevention of cancer recurrence in patients who have had cancer). The NCIC CTG has and will continue to focus on testing interventions for primary (in high-risk individuals) and tertiary prevention.

Specific Categories

5. To develop and evaluate ***new methodologies of clinical trial design, conduct and analysis***. Improving our abilities to obtain high-quality information is required to accurately and efficiently determine whether new interventions bring value.

6. To provide and facilitate ***investigator education and training***. In particular, it is a priority for the NCIC CTG to contribute to assuring that there is a next generation of Canadians who will be international leaders in clinical cancer research.

New Projects and Funding

Projects by Funding Type

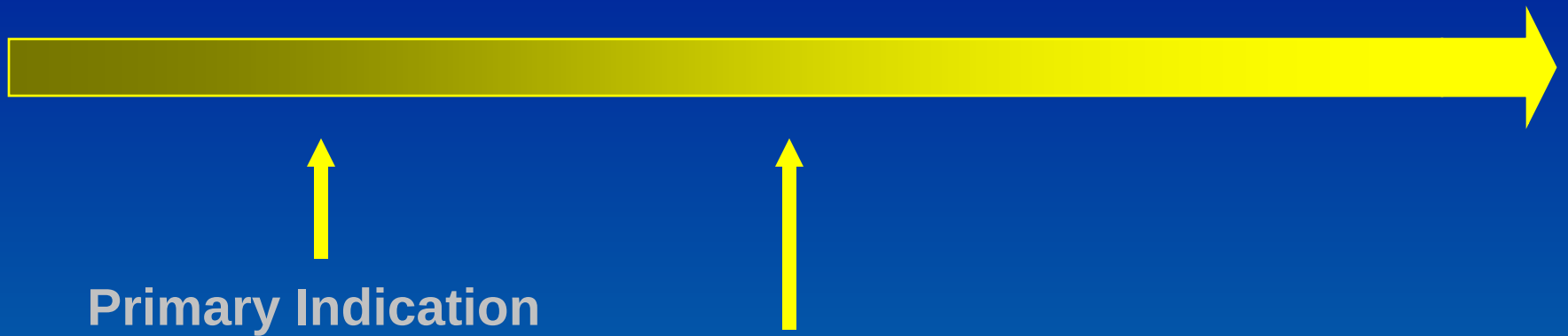
- Industry Contract
- Grant
  - CCSRI
  - Other
- NCI/CTEP (CTSU)

Progression of Trials: Phase 3

Primary Indication ('NDA'):

- Usually led by company
- NCIC CTG somewhat unique
- Always for regulatory
- Complex
- Expensive

Progression of Trials: Phase 3



Primary Indication ('NDA'):

Secondary Indication:

- **Often 'investigator' initiated**
- **Thus, in remit of coop group**
- **Can be for regulatory**
- **Complex, but less so (?)**
- **Expensive**

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Progression of Trials: Phase 3

Primary Indication ('NDA'):

Secondary Indication:

'Better / New' Application:

- Investigator initiated
- In remit of coop group
- Less likely for regulatory
- Can be 'large / simple'
- Expense depends on scope

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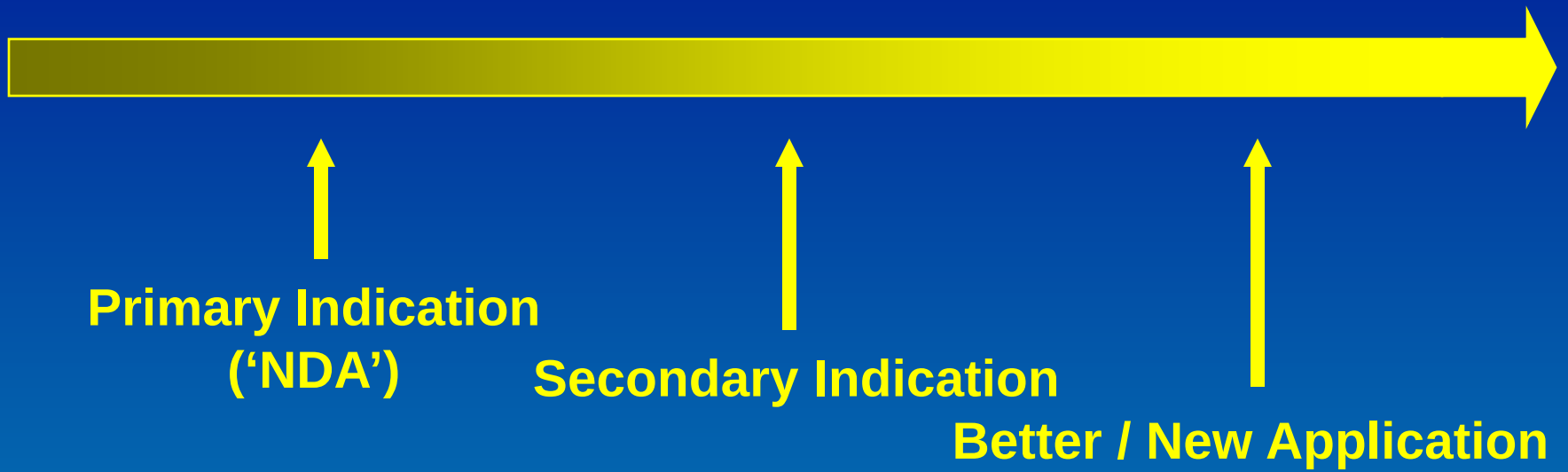
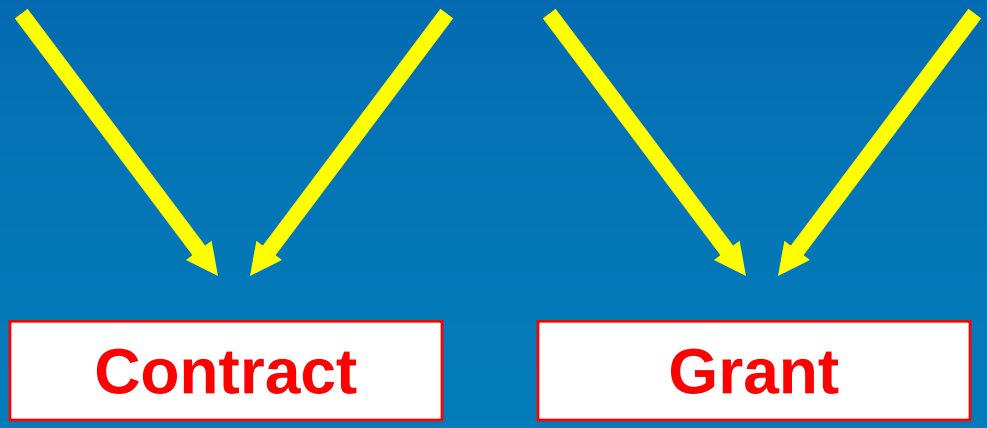
Progression of Trials: Phase 3





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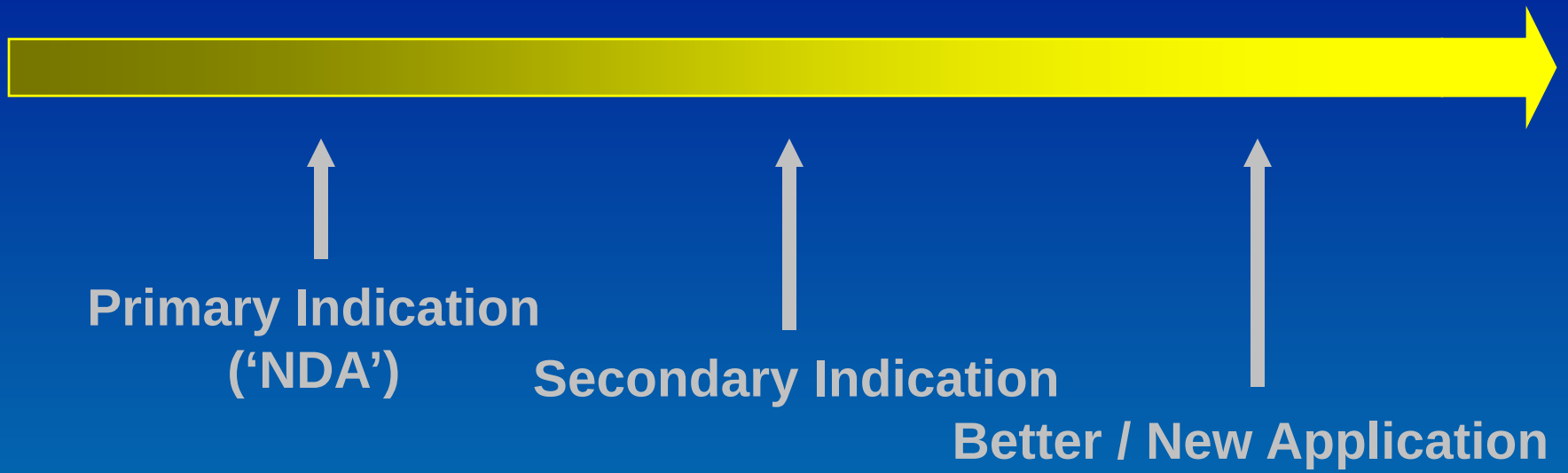
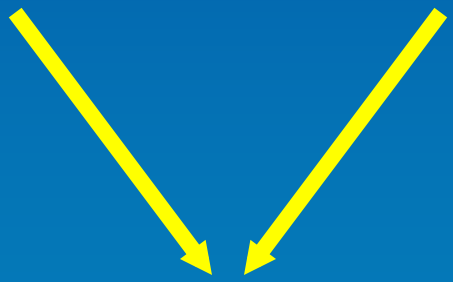
Progression of Trials: Phase 3



- Traditional funding has been CCSRI + overhead
- These sources are now limited
- New sources, and thus new processes, are needed



Grant

How to “Get In”

How to “Get In”

- Come to meetings
- Be active in your centre
- Accrue to trials
- Bring your ideas forward
- Get on a committee
    - Disease Site Committee
    - Let any special backgrounds be known
    - Consider an operations committee
    - (eg Audit / Monitoring)

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How to “Get In”

- Communicate your interest
  - Within centre-to-centre and site reps
  - To us
  - To site chair
- Respond to surveys, questions about studies
- Accrue to active trials
- If medical / heme onc, consider IND trials

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