PMDA 科学委員会
第4回　希少がん対策専門部会
医薬品医療機器総合機構　6階会議室
2017年6月30日 (金) 16:00-18:00

希少がん対策と医薬品開発
～医師として、患者として～

Rare cancers: a sea of opportunity
- How to Create Sustainable Ecosystems with Patient and Public Involvement -

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希少がんサバイバー

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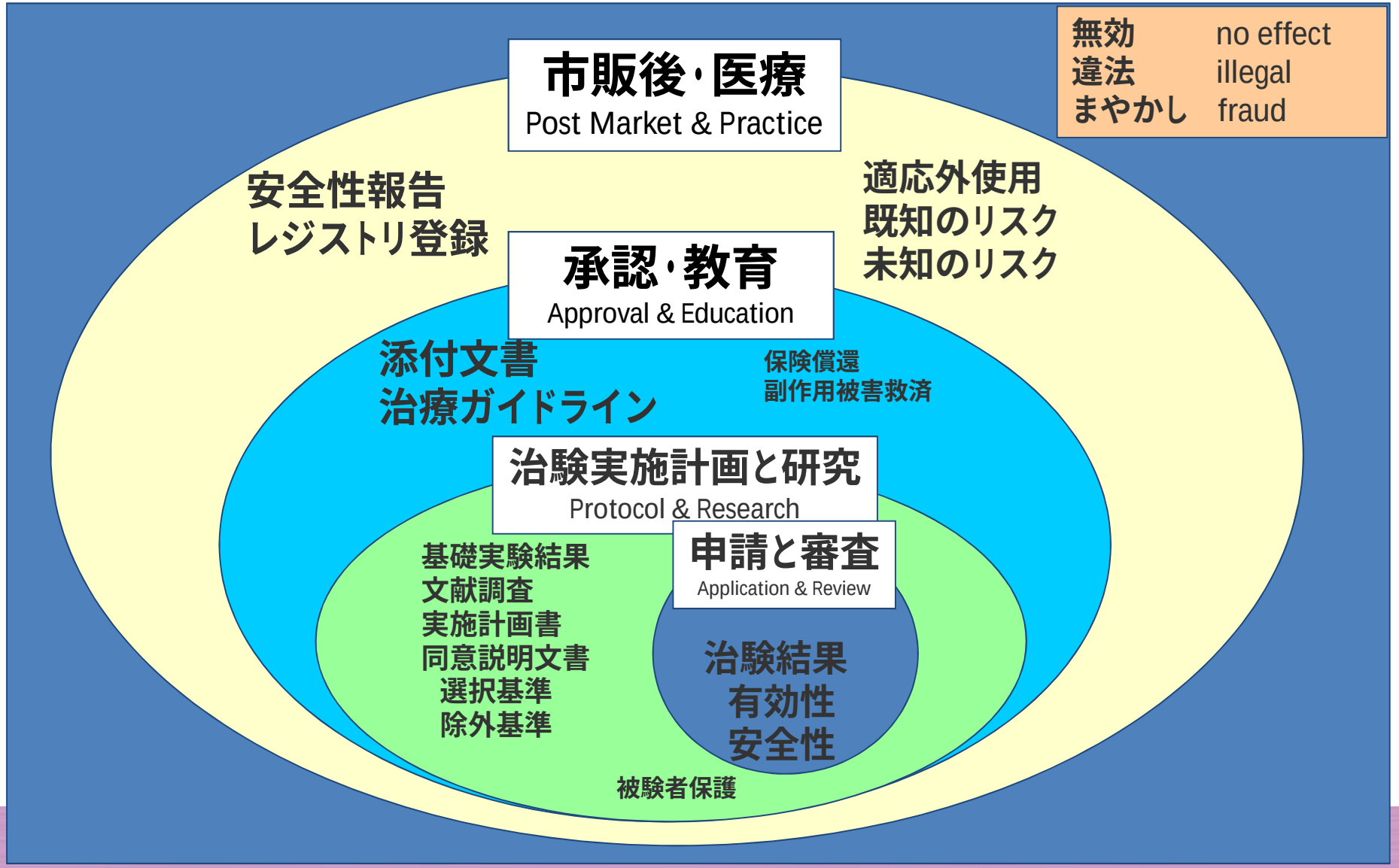
エビデンスを知る(教育)･使う(診療)･創る(研究)
Evidence-based Education, Practice, and Research



PMDA 科学委員会 第4回　希少がん対策専門部会

希少がん対策と医薬品開発～医師として、患者として～

Rare cancers: a sea of opportunity - How to Create Sustainable Ecosystems with Patient and Public Involvement -

- 患者の視点から見た希少がん
  - 医学への敬意
  - 医療への感謝
  - 研究への希望
- レギュラトリー・サイエンスと希少がん
  - プレシジョン・メディシン
  - エビデンスに基づく医療（EBM）
  - リアル・ワールド・エビデンス(RWE)
- 科学委員会への期待
  - 患者中心の医療研究(PCOR)
  - 重要性を増す学際領域

京大病院にて（1986年）

ある日、循環器内科医が「希少がん」と診断されました

手術だけだと余命は半年から2年、抗がん剤が効くかどうかは５０／５０

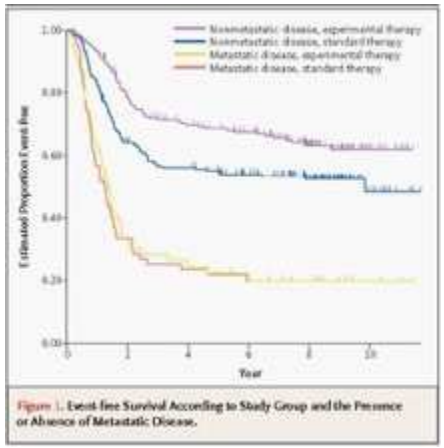
- 飛鳥へ、そしてまだ見ぬ子へ
  - 井村和清　著. 祥伝社: ISBN978-4396101688 (1980)
  - 名高達郎、竹下景子　出演. 東宝映画:　(1982)
  - 稲垣吾郎　出演. フジテレビ：平成17年度文化庁芸術祭参加作品
  - DVD:　EAN4988002491124 (2005)
- 少しは恩返しできたかな
  - 北原美貴子　著. 講談社：ISBN 978-4062127400 (2005)
  - 二宮和也　主演. TBSテレビ: DVD; EAN4582224460076 (2006)
- 君がくれた夏
  - 山崎敏子　著. 小学館：ISBN 978-4094081916 (2007)
  - 「がんばれば、幸せになれるよ」
  - 滝沢秀明、深田恭子　出演. 雨宮望　監督.
  - 日本テレビ：24時間スペシャルドラマ2007「君がくれた夏」
  - DVD: EAN4988021133876 (2007)
- たくさんの愛をありがとう
  - 先間寿子　著. ごま書房：ISBN 978-4341082871 (2005)
  - 桃井かおり　出演、雨宮　望　監督. 日本テレビ
  - DVD: EAN4988021126113 (2007)
- Terry Fox: His Story
  - Scrivener L. McClelland & Stewart (Tronto)
  - ISBN 978-0771080197. (2000)
- Fifty-Fifty
  - ジョセフ・ゴードン=レヴィット、セス・ローゲン出演
  - DVD: EAN4907953042476 (2011)

ちょっと調べてみただけでも、たくさんの
テレビドラマや映画が. . . でもほとんどが悲劇

約2年間にわたる抗がん剤治療と手術は大変でしたが、多くの人に助けられ、とりあえず乗り切ることができました

医学部で習った昔の教科書には、
とても稀なタイプの病気で
患肢を切断しても余命約2年、
などととても厳しいことが
書いてありました

いろいろな先生に相談したところ、
2003年にアメリカの先生達が
発表した論文を基に、手術の前後で
約2年間にわたり約20回入院して
抗がん剤を投与した方が良いという
ことがわかりました



まだまだ日本語の情報は乏しい
ものの、英語のホームページや
最新の医学論文も参考にしつつ、
信頼できる情報や相談相手に
たどり着きました

客観的な事実を冷静に理解し、
主観的な感情を（家族や友人に
助けられながら）徐々に受入れ、
長い治療期間をなんとか
乗り切ることができました

残念ながら、途中で同室になった
患者仲間の一部は、同業の医師を
含め、治療の甲斐無く、亡くなり
ました（涙）

でも、自分よりも辛い状況でも
それぞれの立場で前向きに生きる
姿から、多くのことを学びました

日常生活を取り戻す過程において、
命の大切さ、そして家族や友人の
ありがたさを改めて痛感しました

とりあえず出来る治療は全て終了、
あとは運命に任せるのみですが、
少しでも長く、そして良く生きて、
恩返しができればと思います

教育の機会を頂いた先人達への敬意、
医療を実際に支えて下さる方々への感謝、
そして研究を通じて将来を担う皆さんに希
望を伝えることができれば嬉しく思います

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MEDICAL PROGRESS

Soft-Tissue Sarcomas in Adults

Matthew A. Clark, F.R.A.C.S., Cyril Fisher, F.R.C.Path., Ian Judson, F.R.C.P., and J. Meirion Thomas, F.R.C.S.

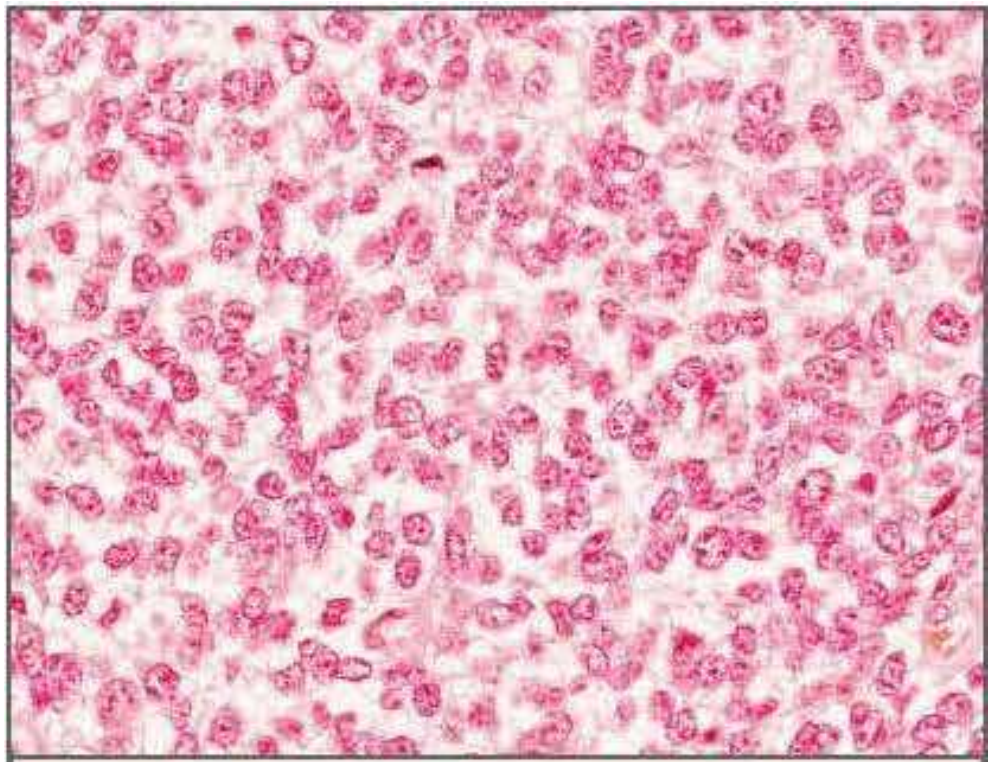


Figure 1. Photomicrograph of Ewing's Sarcoma, a Type of Small Round-Cell Tumor (Hematoxylin and Eosin).

Table 2. Chromosomal Translocations in Soft-Tissue Sarcomas.*

Type of Tumor	Translocation	Genes Involved
Synovial sarcoma	t(X;18)(p11.2;q11.2)	*SSX1* or *SSX2*, *SYT*
Myxoid or round-cell liposarcoma	t(12;16)(q13;p11)	*CHOP*, *TLS*
	t(12;22)(q13;q11-q12)	*CHOP*, *EWS*
Ewing's sarcoma or peripheral primitive neuroectodermal tumor	t(11;22)(q24;q12)	*FLI1*, *EWS*
	t(21;22)(q22;q12)	*ERG*, *EWS*
	t(7;22)(p22;q12)	*ETV1*, *EWS*
	t(2;22)(q33;q12)	*FEV*, *EWS*
	t(17;22)(q12;q12)	*E1AF*, *EWS*
Desmoplastic small round-cell tumor	t(11;22)(p13;q12)	*WT1*, *EWS*
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	*PAX3*, *FKHR*
	t(1;13)(p36;q14)	*PAX7*, *FKHR*
Extraskeletal myxoid chondrosarcoma	t(9;22)(q21-31;q12.2)	*CHN*, *EWS*
	t(9;17)(q22;q11)	*CHN*, *RBP56*
Clear-cell sarcoma	t(12;22)(q13;q12)	*ATF1*, *EWS*
Alveolar soft-part sarcoma	t(X;17)(p11;q25)	*TFE3*, *ASPL*
Dermatofibrosarcoma or giant-cell fibroblastoma	t(17;22)(q22;q13)	*COL1A1*, *PDGFB1*
Infantile fibrosarcoma	t(12;15)(p13;q25)	*ETV6*, *NTRK3*
Low-grade fibromyxoid sarcoma	t(7;16)(q34;p11)	*FUS*, *BBF2H7*

* The translocations should be read, for example, as follows: t(X;18)(p11.2;q11.2) is a translocation between chromosomes X and 18 involving the short arm at region 11.2 and the long arm at region 11.2.

THE EWING FAMILY OF TUMORS — A SUBGROUP OF SMALL-ROUND-CELL TUMORS DEFINED BY SPECIFIC CHIMERIC TRANSCRIPTS

Olivier Delattre, M.D., Ph.D., Jessica Zucman, M.D., Thomas Melot, Xavier Sastre Garau, M.D., Jean-Michel Zucker, M.D., Gilbert M. Lenoir, D.V.M., Peter F. Ambros, Ph.D., Denise Sheer, D.Phil., Claude Turc-Carel, M.D., Timothy J. Triche, M.D., Ph.D., Alain Aurias, M.D., and Gilles Thomas, M.D., Ph.D.

SYT-SSX GENE FUSION AS A DETERMINANT OF MORPHOLOGY AND PROGNOSIS IN SYNOVIAL SARCOMA

SYT-SSX GENE FUSION AS A DETERMINANT OF MORPHOLOGY AND PROGNOSIS IN SYNOVIAL SARCOMA

Kawai NEJM 1998;338:153

Akira Kawai, M.D., Ph.D., James Woodruff, M.D., John H. Healey, M.D., Murray F. Brennan, M.D., Cristina R. Antonescu, M.D., and Marc Ladanyi, M.D.

NCCH

Bone Tumor Registry

Histology	Total	U/E	L/E	Trunk
Solitary bone cyst	194	68	104	20
Aneurysmal bone cyst	37	6	24	7
Fibrous dysplasia	153	22	92	29
Osteoid osteoma	59	10	41	8
Enchondroma	297	196	76	8
Osteochondroma	293	35	151	33
Giant cell tumor	155	25	109	20
Osteosarcoma	205	19	147	28
Chondrosarcoma	95	22	30	38
Ewing/PNET	27	2	9	14
Chordoma	23	-	-	23
Total	3,137	524	1,235	639

Bone Tumor Registry in Japan (2007)

The New England
Journal of Medicine

Volume 248 APRIL 2, 1953 Number 14

EWING'S SARCOMA*

A Study of Fifty Cases Treated at the Massachusetts General Hospital, 1930–1952 Inclusive

C. C. WANG, M.D.,† AND MILFORD D. SCHULZ, M.D.‡

BOSTON

EWING'S sarcoma was first described by James Ewing in 1921.[1,2] Since then a voluminous literature regarding this interesting disease has appeared. The pathogenesis, histology, clinical features, and roentgenographic appearance have been extensively studied.[3-9] The purpose of the present investigation is to analyze a group of patients treated at the Massachusetts General Hospital from 1930 to 1952 inclusive.

Tables 1 and 2 summarize the cases and the results of treatment. Males were slightly predominant in the group — 27 were males, and 23 females.

Table 3 shows the age distribution of the patients at the time of admission to the hospital. The youngest was three and a half years, and the oldest forty-three years of age. Twenty-nine were in the

TABLE 1. *Patients with Ewing's Sarcoma Treated at the Massachusetts General Hospital, 1930–1952.*

Case No.	Sex	Age	Symptoms	Duration	Primary Location	Operation	Result	Period of Survival	Remarks
		yr.							
Group A (treatment with radical surgery):									
1	M	15	Swelling	3 yr.	Radius	Amputation	Dead with disease	40 mo.	
2	M	16	Pain and swelling	3 wk.	Tibia	Low-thigh amputation	Dead with disease	10 mo.	
3	F	23	Pain and swelling	6 mo.	Tarsal	Amputation	Dead with disease	5 mo.	
4	M	20	Pain and swelling	6 wk.	Fibula	Gritti-Stokes amputation	Dead with disease	19 mo.	
5	M	30	Pain	2 yr.	Tibia	Low-thigh amputation	Living without disease	6 yr.	Lost after 6 yr.
6	M	16	Pain and swelling	3 mo.	Fibula	Low-thigh amputation	Dead with disease	4 mo.	
7	F	14	Swelling	2 yr.	Mandible	Resection, rt. lower jaw	Dead with disease	30 mo.	
8	F	34	Pain	1 yr.	Tibia	Low-thigh amputation	Dead with disease	48 mo.	
9	F	13	Swelling	18 mo.	Fibula	Low-thigh amputation	Dead with disease	28 mo.	
10	M	15	Swelling	3 mo.	Fibula	Low-thigh amputation	Dead with disease	6 mo.	
Group B (radical surgery with postoperative irradiation):									
11	M	19	Pain	3 mo.	Sacrum	Excision + 5000 r	Dead with disease	3 mo.	
12	M	20	Pain and swelling	3 mo.	Fibula	Resection + x-ray	Dead with disease	2 mo.	Tumor dose unknown
13	M	18	Pain	4 mo.	Rib	Rib resection + 5000 r	Dead with disease	5 mo.	Irradiation to lt. side of chest
14	F	40	Pain and swelling	4 mo.	Rib	Rib resection + 4000 r	Dead with disease	6 mo.	Irradiation to lt. side of chest

J Cancer Res Clin Oncol (2008) 134:389–395
DOI 10.1007/s00432-007-0295-9

ORIGINAL PAPER

Prediction of response and prognostic factors for Ewing family of tumors in a low incidence population

Kan Yonemori · Umio Yamaguchi · Masayuki Kaneko · Hajime Uno · Masahiro Takeuchi · Masashi Ando · Yasuhiro Fujiwara · Ako Hosono · Atsushi Makimoto · Tadashi Hasegawa · Ryouhei Yokoyama · Fumihiko Nakatani · Akira Kawai · Yasuo Beppu · Hirokazu Chuman

Received: 20 May 2007 / Accepted: 13 July 2007 / Published online: 9 August 2007

Abstract
Purpose There is some unknown reason Ewing family of tumors (EFTs) is much less common on Asia and Africa than in the Western Caucasian population. This study analyzed the prediction of response and prognostic factors for Ewing family of tumors (EFTs) in an Asian population with a low incidence.
Methods We retrospectively reviewed 94 patients with EFTs between 1978 and 2006. Fifteen patients received local therapy only. Statistical analyses were performed for 79 patients, including those who received systemic chemotherapy, to identify factors related to chemotherapy responsiveness, event-free survival, and overall survival.
Results Of the 79 patients whose records were analyzed, the 5-year event-free rate and overall survival (OS) rate were 41 and 54%, respectively. The response rate to first-line chemotherapy was 61% in 70 patients with assessable lesions. A significant predictor of response was existence of a non-pelvic primary tumor ($P = 0.04$). Significant prognostic factors for OS were age, performance status, and metastases at the time of diagnosis ($P < 0.01$, respectively). Fifty-four patients had disease progression or recurrence after first-line treatment. The time to progression was 3.4 months after salvage treatment. Progression during first-line treatment was significantly associated with time to progression after salvage treatment ($P = 0.01$). All patients treated without chemotherapy in first-line treatment were recurred with poor prognosis.
Conclusion A non-pelvic primary tumor was a favorable predictor of responsiveness to chemotherapy. Chemoresistant patients might less benefit from second line chemotherapy. Chemotherapy in first-line treatment should not be omitted, even if primary tumor was extirpated completely.

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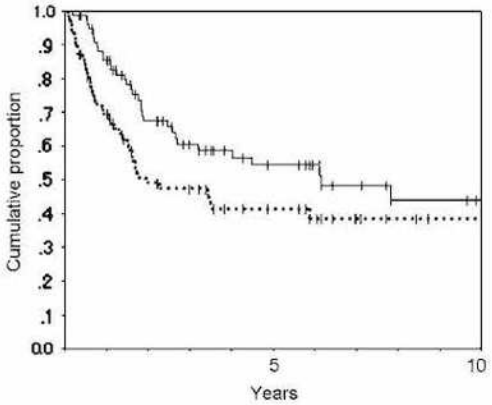

Fig. 1 Kaplan–Meier analysis of event-free survival (*dotted line*) and overall survival (*solid line*) in 79 patients who received chemotherapy. The *vertical bars* indicate censored cases

J Cancer Res Clin Oncol (2008) 134:389–395

Patients treated without chemotherapy in first-line treatment

In this study, 15 patients did not receive chemotherapy as part of their first-line treatments. The median age of these patients was 39 years (range 20–53 years). None of these patients had metastasis, and most of the patients (87%) had extra-osseous primary tumors. Two-thirds of the patients had a primary tumor size ≤80 mm. Nine patients had pelvic primary tumors, and only two patients had primary tumors in their extremities. A univariate analysis indicated that age, percentage of extra-osseous primary tumor sites, and percentage of pelvic primary tumor sites were significantly different among these 15 patients, compared with the other 79 patients. Two-thirds of these cases were admitted during the last 5 years of the study period. Regrettably, all patients had recurred, 13 patients had developed systemic recurrence and the other had local recurrence. The median time to recurrence was 9.4 months. The most common systemic disease sites was lung ($n = 6$), liver ($n = 5$), bone ($n = 4$),

素晴らしい仲間達に恵まれました
しかしながら…

吉野　ゆりえ
大分県竹田市出身。大分県立大分雄城台高等学校、筑波大学第三学群国際関係学類卒業。東京アナウンスアカデミー・アナウンス専攻科修了。元ミス日本。筑波大学入学と同時に競技ダンスを始め、4年生の時にプロに転向。大学卒業後、ダンスの本場イギリスに留学。日本との間を10年間行き来する。その間、国内外の大会で活躍。インターナショナル選手権ライジングスターチャンピオン。全日本選手権ファイナリスト。全日本セグエ選手権ファイナリスト。2006年、視覚障害者のための世界初「第1回全日本ブラインドダンス選手権大会」を開催。「24時間テレビ　愛は地球を救う」（日本テレビ）内で放映される。現在、大会審査員やMC（司会者）として活躍中。世界ダンス議会国際審査員。日本ダンス議会審査員。日本ブラインドダンス協会理事、事務局長。ウリナリ芸能人社交ダンス部特別講師。都立八王子盲学校外部指導員

吉野ゆりえ　さん

- 希少がんである「肉腫（サルコーマ）」の患者
- 日本にサルコーマセンターを設立する会　会長
- 「10年生存」を達成
- 19度の手術と6度の放射線治療
- 2015年から殺細胞性抗がん剤
- 2016年1月から分子標的薬
- 2016年2月半ばに薬剤性心不全
- 2016年7月20日　サバイバーを卒業…

JBPress（2016年4月19日）http://jbpress.ismedia.jp/articles/-/46623

Japan Sarcoma Center Project
日本に「サルコーマセンターを設立する会」
～肉腫（サルコーマ）を「あきらめたガン」でなくすために～

http://www.japan-scp.net/hos.html

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Rare cancers: a sea of opportunity - How to Create Sustainable Ecosystems with Patient and Public Involvement -

- 患者の視点から見た希少がん
  - 医学への敬意
  - 医療への感謝
  - 研究への希望
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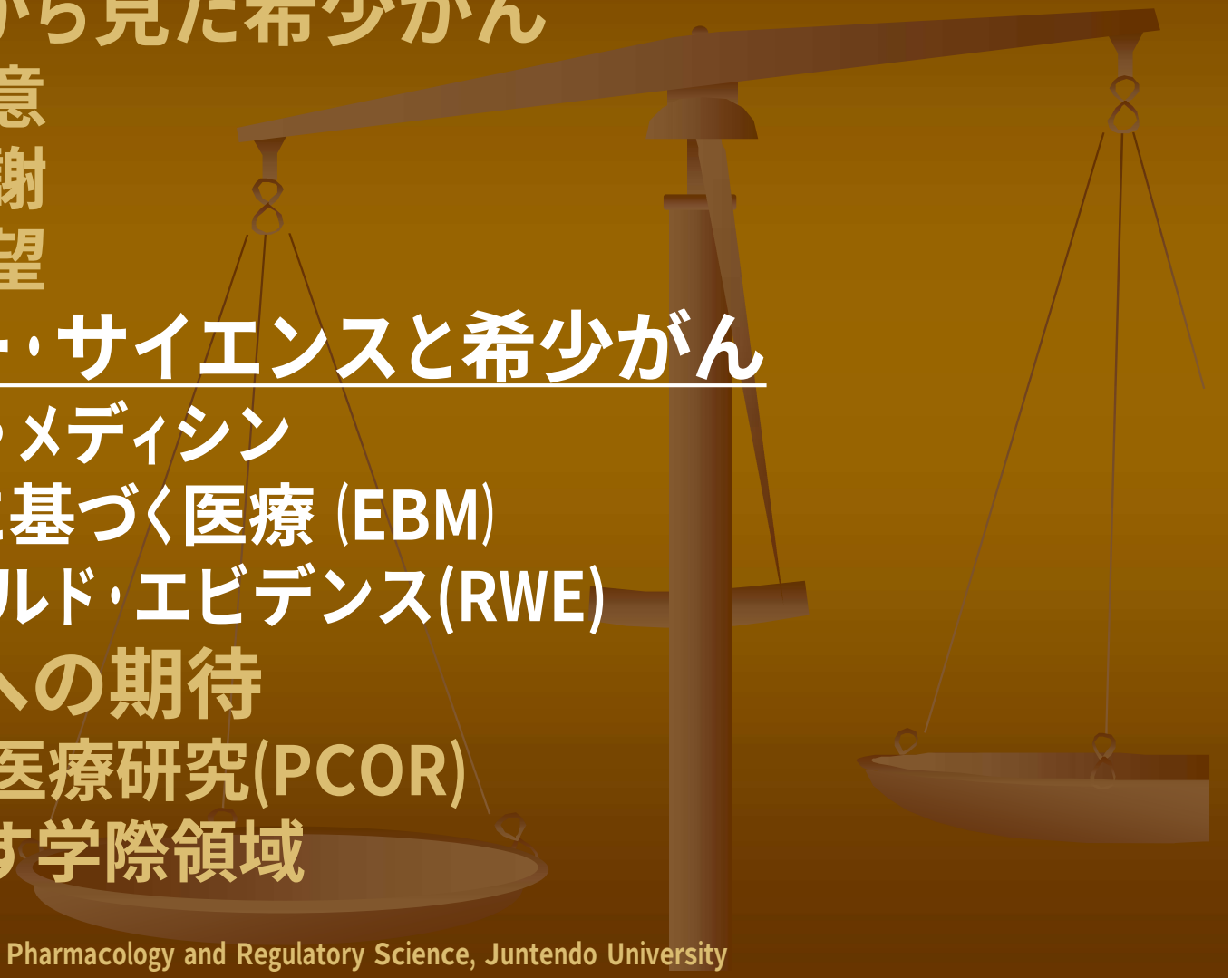

Lancet Oncol 2016;17:e52-61

Rare cancers 1

Rare cancers: a sea of opportunity

Niki Boyd, Janet E Dancey, C Blake Gilks, David G Huntsman

Rare cancers, as a collective, account for around a quarter of all cancer diagnoses and deaths. Historically, they have been divided into two groups: cancers defined by their unusual histogenesis (cell of origin or differentiation state)—including chordomas or adult granulosa cell tumours—and histologically defined subtypes of common cancers. Most tumour types in the first group are still clinically and biologically relevant, and have been disproportionately important as sources of insight into cancer biology. By contrast, most of those in the second group have been shown to have neither defining molecular features nor clinical utility. Omics-based analyses have splintered common cancers into a myriad of molecularly, rather than histologically, defined subsets of common cancers, many of which have immediate clinical relevance. Now, almost all rare cancers are either histomolecular entities, which often have pathognomonic mutations, or molecularly defined subsets of more common cancers. The presence of specific genetic variants provides rationale for the testing of targeted drugs in rare cancers. However, in addition to molecular alterations, it is crucial to consider the contributions of both mutation and cell context in the development, biology, and behaviour of these cancers. Patients with rare cancers are disadvantaged because of the challenge of leading clinical trials in this setting due to poor accrual. However, the number of patients with rare cancers will only increase as more molecular subsets of common cancers are identified, necessitating a shift in the focus of clinical trials and research into these cancer types, which, by epidemiological definitions, will become rare tumours.

Lancet Oncol 2016; 17: e52–61

This is the first in a **Series** of three papers about rare cancers

Department of Molecular Oncology (N Boyd PhD, Prof D G Huntsman MD), **and Department of Pathology and Laboratory Medicine** (Prof C B Gilks MD) **British Columbia Cancer Agency, Vancouver, BC, Canada; Department of Oncology, Queen's University, Kingston, ON, Canada** (Prof J E Dancey); **and Department of Pathology and Laboratory Medicine and Department of Obstetrics and Gynecology, University of British Columbia, Vancouver,**

Oncology trials gear up for high-throughput sequencing

Researchers are starting to use high-throughput genomic technologies to guide patients into trials of experimental cancer therapies, but is our understanding of the cancer genome ready yet?

CANCER GENOMICS

Constructing a 'cancerpaedia'

Many of us have tried to explain our research projects to a friend or relative and ended up summarizing with the unsatisfactory phrase, "well, it's…complicated". That message is all too applicable in the translation of genomic findings in cancer cell lines to clinical therapies, but two recent papers in *Nature* aim to help by constructing encyclopaedias of cell lines and drug interactions.

The two groups of researchers each assembled a panel of hundreds of cancer cell lines and characterized multiple genomic features, gene expression and copy number variation. Each group then conducted a screen with anticancer drugs and used various bioinformatic analyses to correlate drug activity with changes in one or more genes. Barretina *et al.* profiled 24 drugs in 479 cell lines, and Garnett *et al.* profiled 130 drugs on 275–507 lines. The results showed a number of known interactions between gene mutations and drug sensitivities — such as changes in *BRAF* associated with RAF inhibitors — but several previously unseen connections emerged immediately.

For example, Barretina *et al.* showed that mutations in *NRAS* in some cell lines lead to sensitivity to MEK-inhibiting drugs through elevating expression of the aryl hydrocarbon receptor (*AHR*) gene. These findings could potentially be applied to the clinic by using expression levels of *AHR* as a biomarker for use of MEK inhibitors instead of *NRAS* mutations.

In addition to single-gene effects, Garnett *et al.* modelled interactions between drug response and multiple genes or transcripts at the same time. They found that general sensitivity to MEK inhibitors recurrently associated with 67 gene or transcript changes, and subsets of cancer cell lines had distinct patterns of biomarkers that should prove to be fruitful for further mechanistic research. Notably, in some cases, transcript levels were markers for drug sensitivity in cell lines without known sensitizing mutations.

An unexpected 'winner' from both efforts is the rare cancer Ewing's sarcoma. Garnett and colleagues found that Ewing's sarcoma cells were very sensitive to poly(ADP-ribose) polymerase (PARP) inhibitors, suggesting that these drugs could be explored as a treatment. Many current PARP inhibitor regimes use the drug with chemotherapy or radiation, but in Ewing's sarcoma cells, the PARP inhibitors were effective killers on their own. Barretina and colleagues found that, of the cell lines tested, Ewing's sarcoma cells were the most sensitive to several chemotherapy drugs. They also found that the expression level of schlafen family member 11 (*SLFN11*), which encodes a cell cycle control protein, is the top predictor of drug response across cell lines and that the Ewing's sarcoma lines were the cell lines that showed the highest expression of *SLFN11*. The authors suggest that expression levels of this gene might be useful in stratifying patients with Ewing's sarcoma (and other cancers) in ongoing trials of some conventional chemotherapy drugs.

Ultimately, of course, the real winners need to be patients with cancer. Both groups have posted their data sets online, in the hope that the community will treat these results as an open encyclopaedia.

Chris Gunter,
Hudson Alpha Institute for Biotechnology

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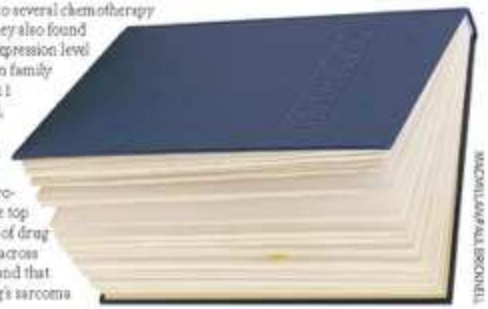
The author declares no competing financial interests.

ORIGINAL RESEARCH PAPERS Barretina, J. *et al.* The Cancer Cell Line Encyclopedia enables predictive modelling of anticancer drug sensitivity. *Nature* **483**, 603–607 (2012) | Garnett, M. J. *et al.* Systematic identification of genomic markers of drug sensitivity in cancer cells. *Nature* **483**, 570–575 (2012)

FURTHER INFORMATION Genomics of Drug Sensitivity in Cancer project: http://www.cancerrxgene.org | Cancer Cell Line Encyclopedia: http://www.broadinstitute.org/ccle/home



MACMILLAN/PAUL BROWNE

Olaparib in Adults With Recurrent/Metastatic Ewing's Sarcoma

This study is not yet open for participant recruitment.

First Received on April 18, 2012. Last Updated on April 23, 2012

Sponsor: Massachusetts General Hospital

- ClinicalTrials.gov Identifier: NCT01583543
- Purpose This research study is a Phase II clinical trial to test the efficacy of Olaparib in adult participants with recurrent/metastatic Ewing's Sarcoma following failure of prior chemotherapy.
- Condition Intervention
- Phase Ewing's Sarcoma Drug: Olaparib Phase 2
- Study Type: Interventional
- Study Design: Endpoint Classification: Efficacy Study
- Intervention Model: Single Group Assignment
- Masking: Open Label
- Primary Purpose: Treatment
- Official Title:

  Phase II Study of the PARP Inhibitor, Olaparib, in Adult Patients With Recurrent/ Metastatic Ewing's Sarcoma Following Failure of Prior Chemotherapy
- Resource links provided by NLM:
- MedlinePlus related topics: Soft Tissue Sarcoma
- U.S. FDA Resources

Lancet Oncol 2016;17:e62-69

Rare cancers 2

The value of research collaborations and consortia in rare cancers

Jean-Yves Blay, Jean-Michel Coindre, Françoise Ducimetière, Isabelle Ray-Coquard

Rare cancers are defined by an incidence of less than six per 100 000 people per year. They represent roughly 20% of all human cancers and are associated with worse survival than are so-called frequent tumours, because of delays to accurate diagnosis, inadequate treatments, and fewer opportunities to participate in clinical trials (because of a paucity of dedicated trials from both academic and industrial sponsors). In this Series paper, we discuss how these challenges can be addressed by research consortia and suggest the integration of these consortia with reference networks, which gather multidisciplinary expert centres, for management of rare tumours.

Lancet Oncol 2016; 17: e62–69

This is the second in a **Series** of three papers about rare cancers

Centre Léon Bérard Lyon and Université Claude Bernard Lyon I, Lyon, France (Prof J-Y Blay MD, F Ducimetière PhD, I Ray-Coquard MD); **Institut Bergonie, Bordeaux, France** (Prof J-M Coindre MD); **Equipe 17 INSERM CRCL, LYRIC (INCA-DGOS 4664), NetSARC, RREPS, and EuroSARC (FP7-278742), Lyon, France** (Prof J-Y Blay); **and European Organisation for Research and Treatment of Cancer, Lyon, France** (Prof J-Y Blay)

Introduction

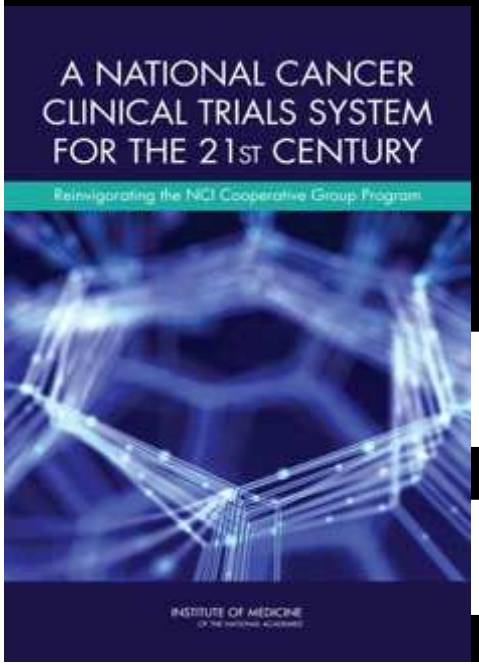
Rare diseases are often defined by their prevalence, with a cutoff that varies from 0·5 to 2 per 1000 in the general population. Although this definition could be applied to rare cancers, it is often deemed inaccurate because it does not take into account the often short life expectancies associated with some rare cancers.[1] A frequent disease associated with a short life expectancy, could inadvertently be classed as a rare disease, because

programmes) and reference networks (which organise the optimum management of patients in routine settings) for the management of rare cancers.

Reference networks and diagnostic accuracy

Management of rare cancers poses specific problems, including delays in diagnosis due to poor diagnostic precision, and therapeutic mismanagement.[1–3] The experience of the medical team and their awareness of rare

Fig1. Structure of Programs (Before)



NCI Division of Extramural Activities (DEA) Review

ECOG
CALGB
SWOG
ACOSOG
COG
RTOG
GOG
ACRIN
NCCTG
NSABP

Disease Committees
Operations
Stats & Data Managements
Tumor Banks

NCI Disease Steering Committees
– Evaluation / Prioritization of Group Trials

NCI Central IRB

Central Access to NCI Clinical Trials Portfolio
(NCI Cancer Trials Support Unit – CTSU)

Cancer Centers
Other Academic Centers
CCOP(s)
Community Practices
International Members

Fig 2. Organizational Structure (New) National Clinical Trials Network

CTAC Clinical Trials Strategic Planning Subcommittee

NCI Disease / Imaging Steering Committees: Evaluation / Prioritization of Trials

Network

Network Imaging and RT Core Services

Network Integrated Translational Components

Tumor Banks

NCI

Canadian Network

4 Adult & 1 Pediatric Network Groups

Adult Group #1 Ops & Stats

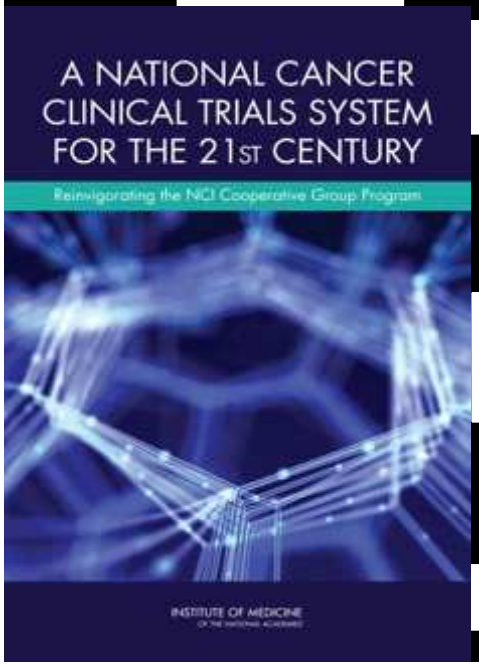
Pediatric Ops & Stats

Adult Group #2 Ops & Stats

Adult Group #4 Ops & Stats

Adult Group #3 Ops & Stats

NCI Clinical Trials Network



Administrative Support Services

NCI Central IRB

CTSU

Central Access to NCI Clinical Trials (Cancer Trials Support Unit)

Network Lead Academic Participating Sites

CCOPS & MB-CCOPs

Other Academic Centers

Community Practices

International Members

Lancet Oncol 2016;17:e70-80

Rare cancers 3

Research methods to change clinical practice for patients with rare cancers

Lucinda Billingham, Kinga Malottki, Neil Steven

Rare cancers are a growing group as a result of reclassification of common cancers by molecular markers. There is therefore an increasing need to identify methods to assess interventions that are sufficiently robust to potentially affect clinical practice in this setting. Methods advocated for clinical trials in rare diseases are not necessarily applicable in rare cancers. This Series paper describes research methods that are relevant for rare cancers in relation to the range of incidence levels. Strategies that maximise recruitment, minimise sample size, or maximise the usefulness of the evidence could enable the application of conventional clinical trial design to rare cancer populations. Alternative designs that address specific challenges for rare cancers with the aim of potentially changing clinical practice include Bayesian designs, uncontrolled n-of-1 trials, and umbrella and basket trials. Pragmatic solutions must be sought to enable some level of evidence-based health care for patients with rare cancers.

Introduction

There are no fixed criteria for the definition of a rare cancer, but a malignant disorder that has an incidence of six or less per 100 000 people per year is commonly classed as rare.[1] Investigation of treatments for rare cancers is important—collectively more than 20% of all

Challenges of conventional trials in rare cancer

The conventional phase 3 clinical trial design for affecting clinical practice is a hypothesis-testing randomised controlled trial with parallel-group treatment comparisons. Such trials are at the highest level of the hierarchy of evidence for assessing the

Lancet Oncol 2016; 17: e70–80

This is the third in a **Series** of three papers about rare cancers

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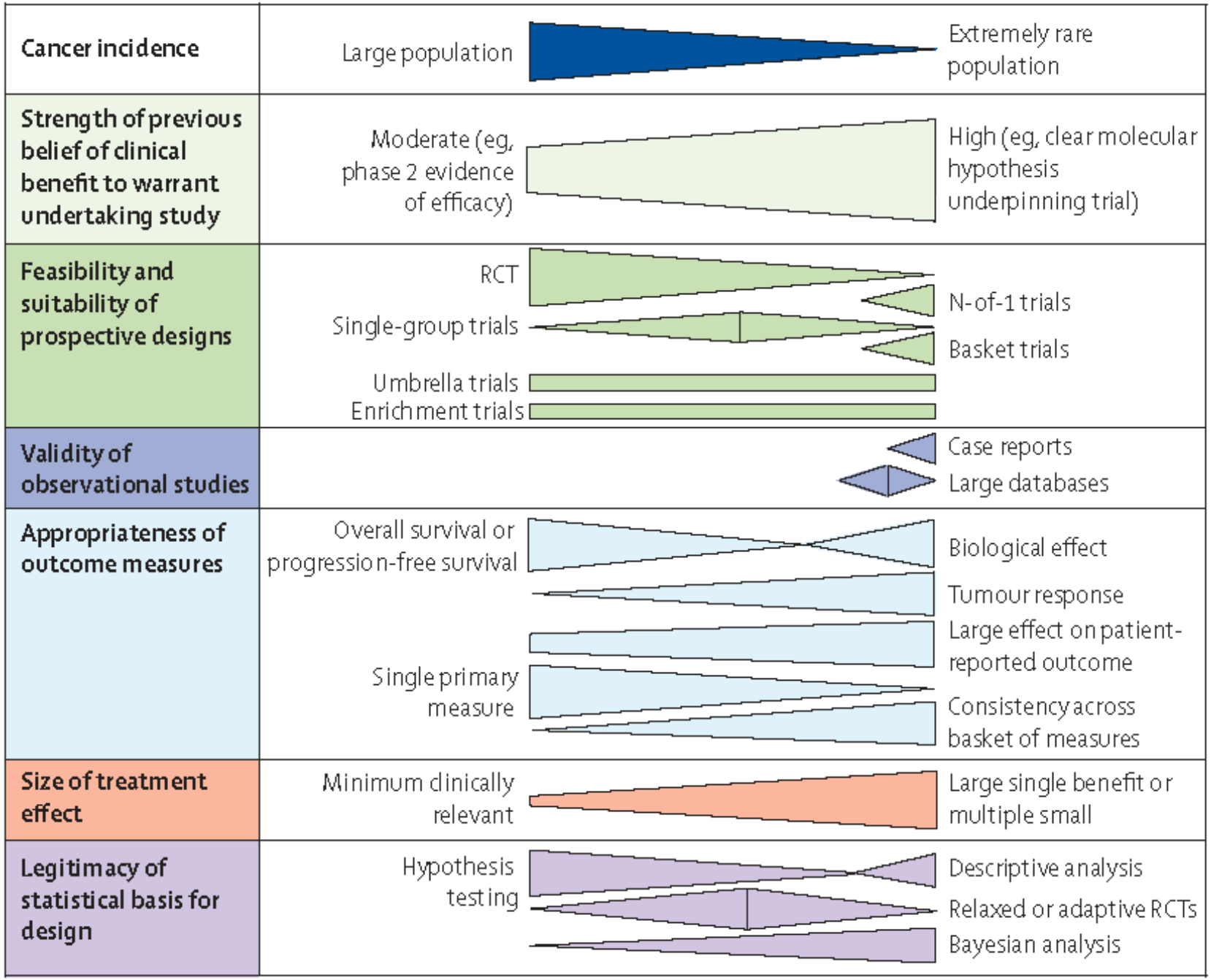
L.J.Billingham@bham.ac.uk


Cancer incidence
Large population
Extremely rare population
Strength of previous belief of clinical benefit to warrant undertaking study
Moderate (eg, phase 2 evidence of efficacy)
High (eg, clear molecular hypothesis underpinning trial)
Feasibility and suitability of prospective designs
RCT
N-of-1 trials
Single-group trials
Basket trials
Umbrella trials
Enrichment trials
Validity of observational studies
Case reports
Large databases
Appropriateness of outcome measures
Overall survival or progression-free survival
Biological effect
Tumour response
Large effect on patient-reported outcome
Single primary measure
Consistency across basket of measures
Size of treatment effect
Minimum clinically relevant
Large single benefit or multiple small
Legitimacy of statistical basis for design
Hypothesis testing
Descriptive analysis
Relaxed or adaptive RCTs
Bayesian analysis

2017

再生医療等製品の実用化に対応した承認制度
(条件・期限付承認)

N Engl J Med 2016; 375:2293-2298

【従来の承認までの道筋】

臨床研究 → 治験 (有効性、安全性の確認) → 承認 → 市販

【再生医療等製品の早期の実用化に対応した承認制度】

※患者のアクセスをより早く！

臨床研究 → 治験 (有効性の推定、安全性の確認) → 条件・期限を付して承認 → 市販 (市販後に有効性、さらなる安全性を検証) → 期限内に再度承認申請 → 承認又は条件・期限付承認の失効 → 引き続き市販

患者にリスクを説明し同意を得、市販後の安全対策を講じる。

https://www.pmda.go.jp/files/000205439.pdf

PMDA 科学委員会 第4回　希少がん対策専門部会

希少がん対策と医薬品開発～医師として、患者として～

Rare cancers: a sea of opportunity - How to Create Sustainable Ecosystems with Patient and Public Involvement -

- 患者の視点から見た希少がん
  - 医学への敬意
  - 医療への感謝
  - 研究への希望
- レギュラトリー・サイエンスと希少がん
  - プレシジョン・メディシン
  - エビデンスに基づく医療（EBM）
  - リアル・ワールド・エビデンス(RWE)
- 科学委員会への期待
  - 患者中心の医療研究(PCOR)
  - 重要性を増す学際領域

pcori | PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

1828 L STREET NW, SUITE 900
WASHINGTON, DC 20036
202.827.7700

Research Done Differently®

The Patient-Centered Outcomes Research Institute (PCORI) takes a different approach to research, one that

- Focuses on research topics, questions and **outcomes most important to patients** and those who care for them.
- Works closely with a **range of healthcare stakeholders**— including patients, caregivers, scientists, clinicians, health systems, and insurers—to guide our research funding.
- Requires that **patients be engaged** in the research we fund, not as subjects but as partners who help determine what to study and how.

This new approach is called
PATIENT-CENTERED OUTCOMES RESEARCH, OR PCOR.

By engaging the end users of study results throughout the research process, we are more likely to focus on asking the right questions, study the outcomes that matter most to patients, and produce the useful and relevant results that are more likely to be used in practice.

CHANGING THE CULTURE OF RESEARCH

Since we began funding research in 2012, our approach to research has fueled a rapid increase in patient-centered research and collaborations among patients, family caregivers, clinicians, researchers, health system leaders, and other healthcare stakeholders. In the process, we're spurring a change in the culture of research from being researcher-driven to stakeholder-driven.

We believe that PCORI's leadership in patient and stakeholder engagement is one of the key reasons this trend is accelerating throughout the research and health policy arenas. In just the past few years:

- Institutions such as Geisinger Health System have been revamping their research processes to include patients and enhance engagement.
- The U.S. Food and Drug Administration announced its first patient engagement advisory committee in 2015.
- The National Institutes of Health has welcomed robust involvement of patients in the Precision Medicine Initiative.

"It's difficult to imagine research without engaging patients and caregivers and other stakeholders anymore. That's a cultural shift that PCORI's responsible for."

—Victor Montori, MD, professor of medicine, Mayo Clinic

"As part of the reexamination of our strategic plan, we formed a working group to explore patient engagement in research and to answer the question of how we could best take advantage of the opportunities that working with PCORI offered us."

—Marc S. Williams, MD, director, Genomic Medicine Institute, Geisinger Health System

"[PCORI has] made it very clear that we are partners in this. It isn't that they're the researchers and we're just the parents. [It's] that we're equals in this."

—Andrea Jensen, patient caregiver

PROJECTS, BY CONDITION*

Mental/ Behavioral Health	43
Cancer	40
Cardiovascular Health	26
Rare Disease	21
Nutritional and Metabolic Disorders	20

**Top five by primary condition; for more, see pcori.org*

PROJECTS, BY POPULATION*

Racial/Ethnic Minorities	237
Low Socioeconomic Status	162
Older Adults	110
Women	95
Children	69

**Projects may cover more than one population; for more, see pcori.org*

As of March 2017, PCORI has awarded around

$1.68 BILLION TO FUND NEARLY 580

CER studies and related projects to enhance the methods and infrastructure to support PCOR

Our research funding includes **$1.2 billion** to support patient-centered studies comparing two or more healthcare options, and another **$120 million** for research to improve the science and methods of CER.

We've Invested $300 million to develop PCORnet®, the National Patient-Centered Clinical Research Network, a **resource for conducting faster, more efficient health research** by harnessing data representing roughly 145 million patients and partnerships among hundreds of patients, clinicians, and healthcare organizations.

pcornet

In addition to our research funding, we've provided another $35 million to support projects and activities to stimulate partnerships, grow communities engaged in PCOR, and nurture ideas for PCOR into study proposals.

U.S. Department of Health and Human Services

http://www.fda.gov/Drugs/NewsEvents/ucm513031.htm

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Drugs

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FDA Public Workshop: Cardiovascular Toxicity Assessment in Oncology Trials

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

Organized by the:
U.S. Food & Drug Administration (FDA)
with support from the American Association for Cancer Research (AACR), American College of Cardiology (ACC), the American Heart Association (AHA) & American Society of Clinical Oncology (ASCO)

Co-Chairs: Dr. Laleh Amiri-Kordestani and Dr. Ana Barac

This Food and Drug Administration (FDA) public workshop will provide a forum for discussion of cardiovascular toxicity assessment within oncology clinical trials. Cardiotoxicity is a well-established complication of oncology therapies. In the past decade, an explosion of novel cancer therapies, often targeted and more specific than conventional therapies, has revolutionized oncology therapy and dramatically changed cancer prognosis. However, some of these therapies have introduced an assortment of cardiovascular complications. At times, these devastating outcomes have only become apparent after drug approval and have limited the use of potent therapies. There is a growing need for better nonclinical testing platforms, imaging and serum biomarkers and trial designs; to screen, monitor and prevent these toxicities. The goals of this public workshop are to:

- Discuss *in vitro* and *in vivo* nonclinical models to assess cardiovascular toxicity.
- Discuss best practices for identifying cardiovascular safety signals within oncology clinical trials.

Cardio-Oncology: Workshop @ FDA (2016)

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  - 重要性を増す学際領域

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