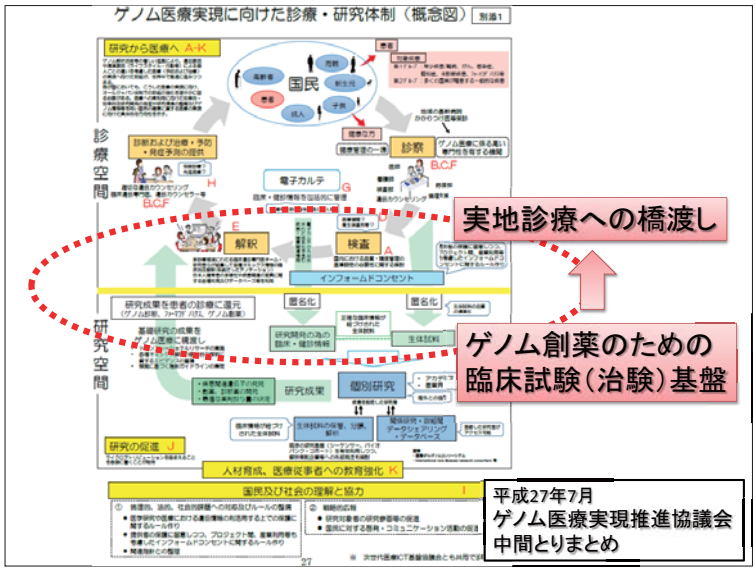
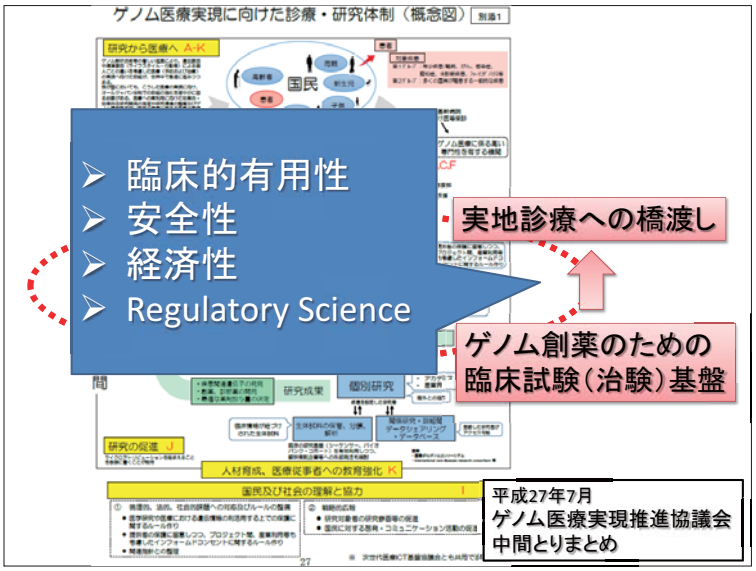
第17回　浜松オンコロジーフォーラム
2015.10.24

新規抗がん治療開発のための全国規模の産学連携遺伝子スクリーニング

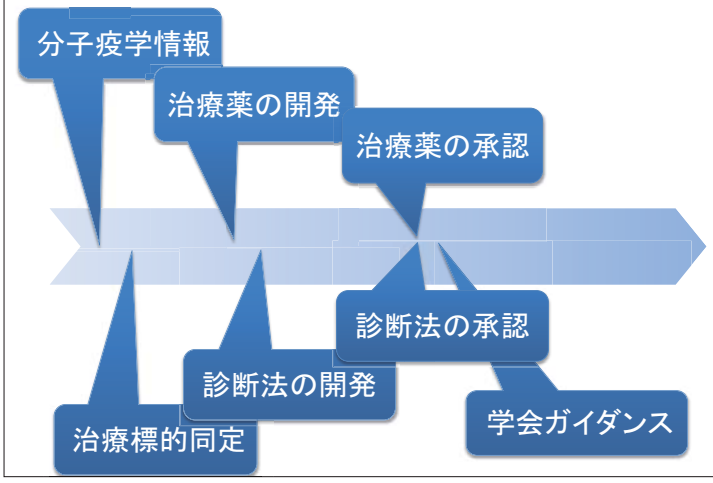
土原 一哉
国立がん研究センター　先端医療開発センター（EPOC）
トランスレーショナルリサーチ分野

Precision Medicine
精密医療
最適化医療

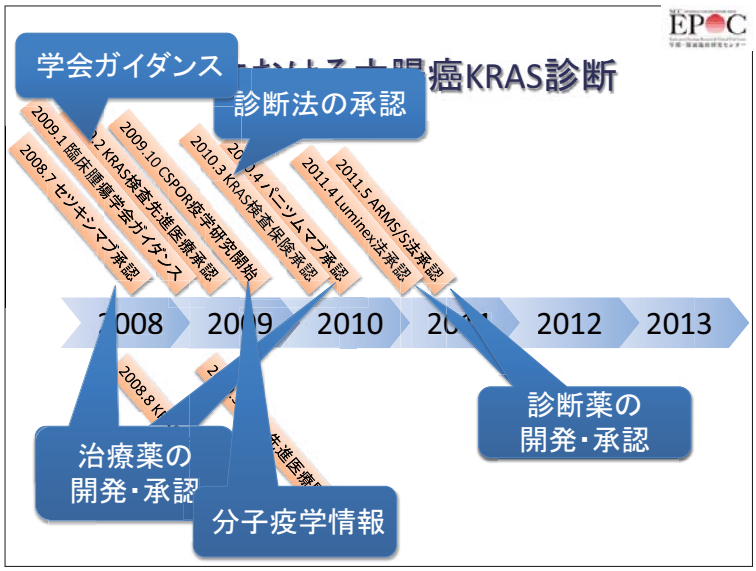




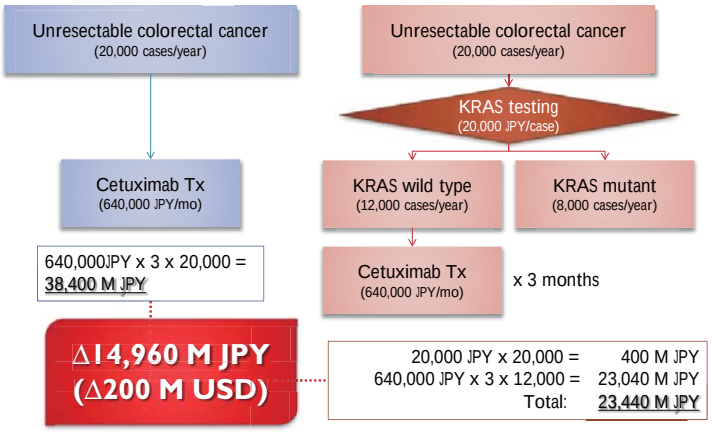
(理想的な)最適化医療開発プロセス

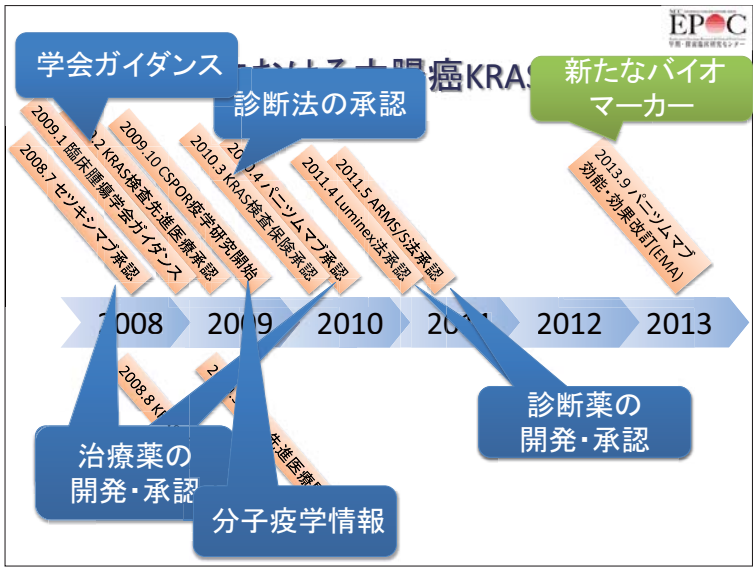


日本における大腸癌KRAS診断



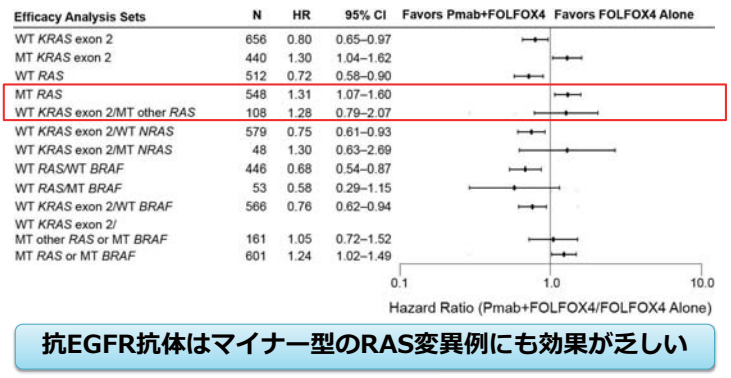
大腸がんKRAS検査による医療経済効果





*RAS*変異型大腸がんに対する抗EGFR抗体薬のエビデンス

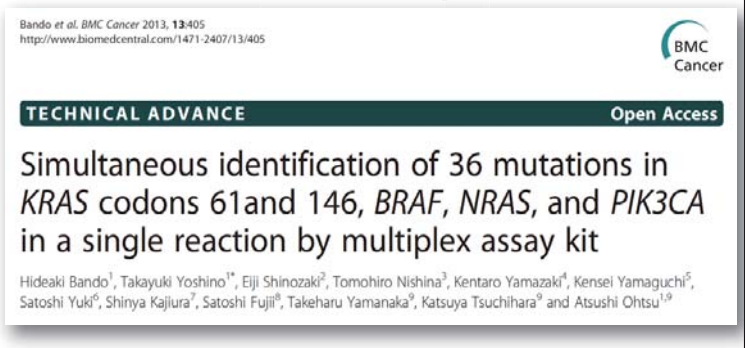
PFS Subgroup Analysis in the PRIME study



抗EGFR抗体はマイナー型のRAS変異例にも効果が乏しい

Douillard JY, et al New Engl J Med 2013

Impact of Minor RAS Mutations;
A Retrospective Analysis with Japanese Cohort of Clinical Settings



Bando *et al. BMC Cancer* 2013, **13**:405
http://www.biomedcentral.com/1471-2407/13/405

BMC Cancer

TECHNICAL ADVANCE Open Access

Simultaneous identification of 36 mutations in *KRAS* codons 61and 146, *BRAF*, *NRAS*, and *PIK3CA* in a single reaction by multiplex assay kit

Hideaki Bando[1], Takayuki Yoshino[1*], Eiji Shinozaki[2], Tomohiro Nishina[3], Kentaro Yamazaki[4], Kensei Yamaguchi[5], Satoshi Yuki[6], Shinya Kajiura[7], Satoshi Fujii[8], Takeharu Yamanaka[9], Katsuya Tsuchihara[9] and Atsushi Ohtsu[1,9]

Impact of Minor RAS Mutations;
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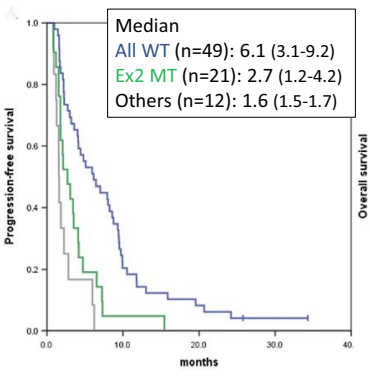
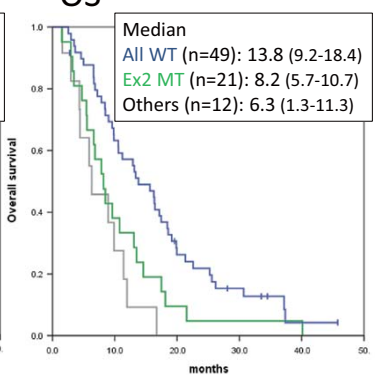
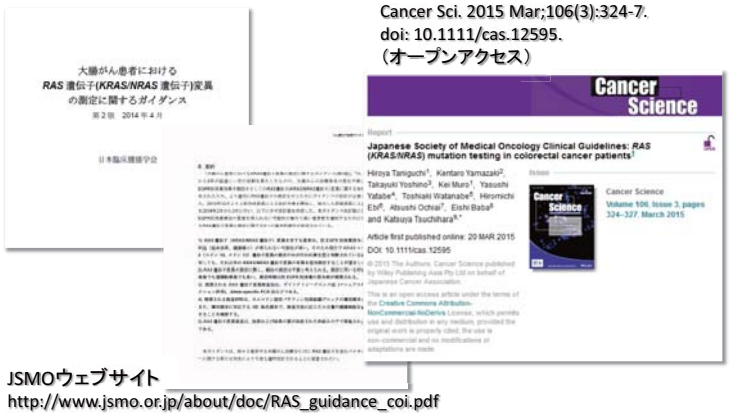
PFS



OS

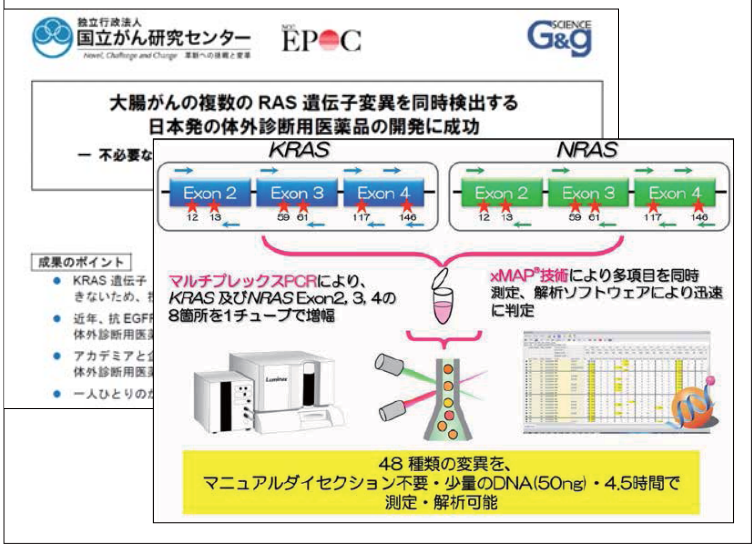


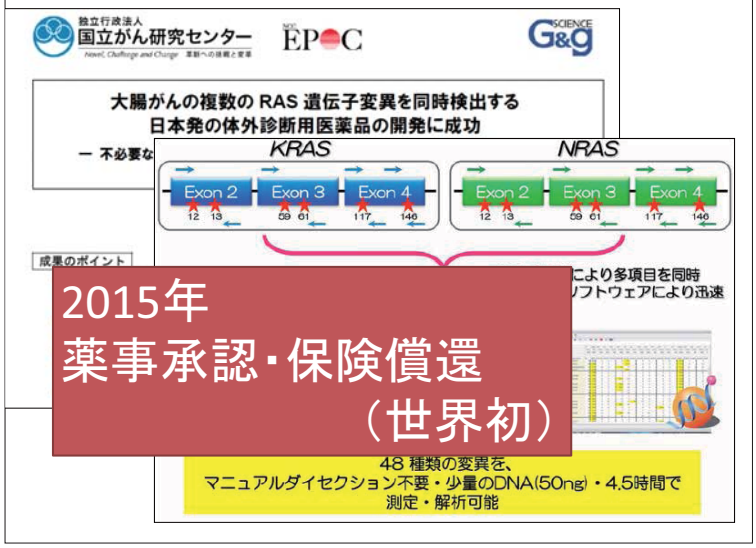
日本臨床腫瘍学会
大腸がんRAS遺伝子変異検査ガイダンス



Cancer Sci. 2015 Mar;106(3):324-7.
doi: 10.1111/cas.12595.
（オープンアクセス）

JSMOウェブサイト
http://www.jsmo.or.jp/about/doc/RAS_guidance_coi.pdf





2015年
薬事承認・保険償還
（世界初）

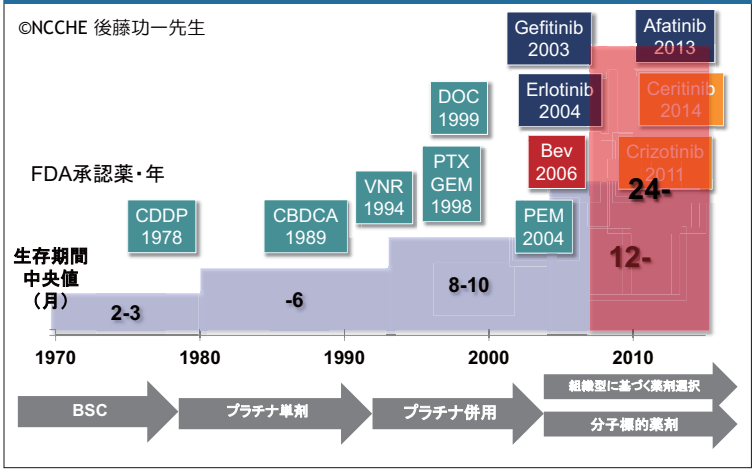
がん薬物療法を最適化するには

- 良質な臨床情報が附随した分子疫学情報
- がんの多様性を反映した非臨床実験系
- グローバルの開発競争の先頭にたつ
  - いち早く情報を収集，情報の良否を吟味する
- バイオマーカー診断の均てん化
  - 全国どこにいても良質な検査が受けられる
- 小回りのきく診断開発
  - 実地臨床に即した診断キットのカスタマイズ

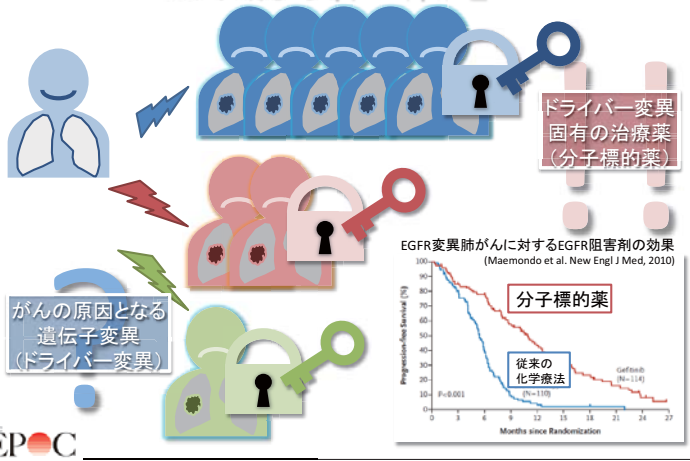
基礎・臨床研究者、治療薬・診断薬メーカーの緊密な連携

NATIONWIDE GENOME SCREENING OF LUNG CANCER; LC-SCRUM JAPAN

進行非小細胞肺癌に対する薬物治療の進歩



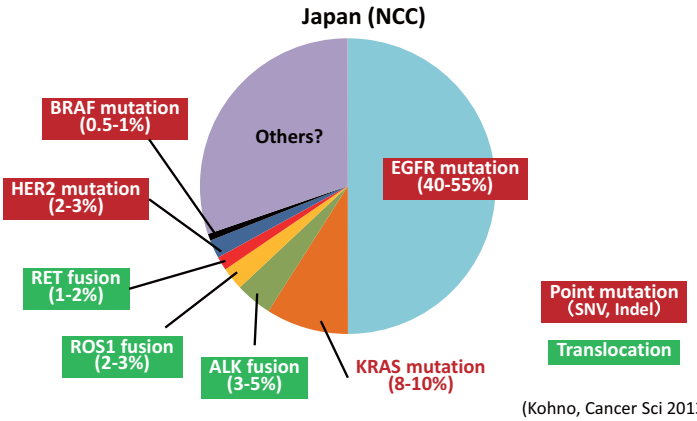
がんのカギ穴(遺伝子変異)に カギ(分子標的薬)を！



EGFR変異肺がんに対するEGFR阻害剤の効果
(Maemondo et al. New Engl J Med, 2010)

EPOC

Stratified Actionable Mutations in Lung Adenocarcinoma



(Kohno, Cancer Sci 2013)

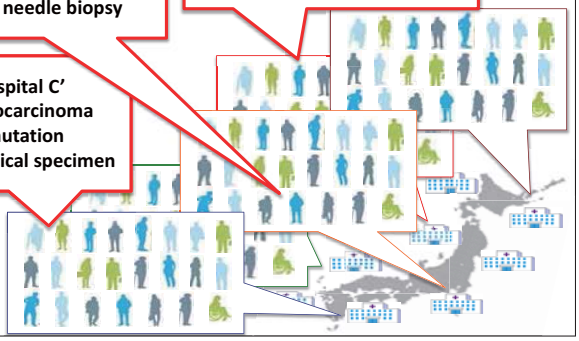
"A Needle in a Haystack"

We have a magic bullet for Gene X-mutated cancer…

Case A at Hospital A'
- Lung adenocarcinoma
- Gene X-gene Y fusion
- Plural effusion

Case B at Hospital B'
- Breast cancer
- Gene X amplification
- Fine needle biopsy

Case C at Hospital C'
- Cholangiocarcinoma
- Gene X mutation
- FFPE surgical specimen



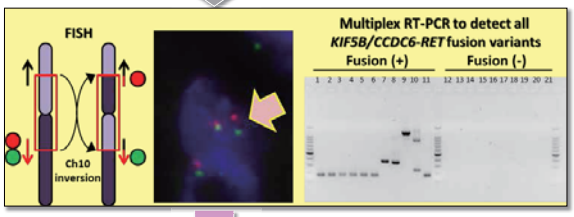
Lung Cancer Genomic Screening Project for Individualized Medicine in Japan (LC-SCRUM-Japan)

A prospective observational study to determine the pathological and molecular characteristics of RET fusion positive lung cancer

- Non-Sq NSCLC, EGFR mutation (-)
- Sample: 1) Fresh Frozen + FFPE or 2) Pleural Effusion

Submit to the ISO15189 certified Lab

3 Fusion Genes
- RET
- ROS1
- ALK



RET fusion gene double positive by RT-PCR & FISH

Phase II Study of Vandetanib for RET Positive NSCLC (LURET study)

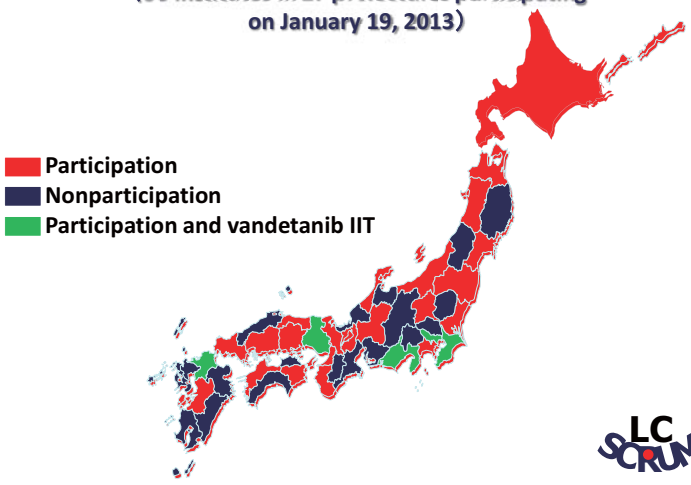
LC SCRUM

January 19, 2013

LC-SCRUM-Japan/LURET study
Kick-off meeting in Tokyo

LC-SCRUM-Japan

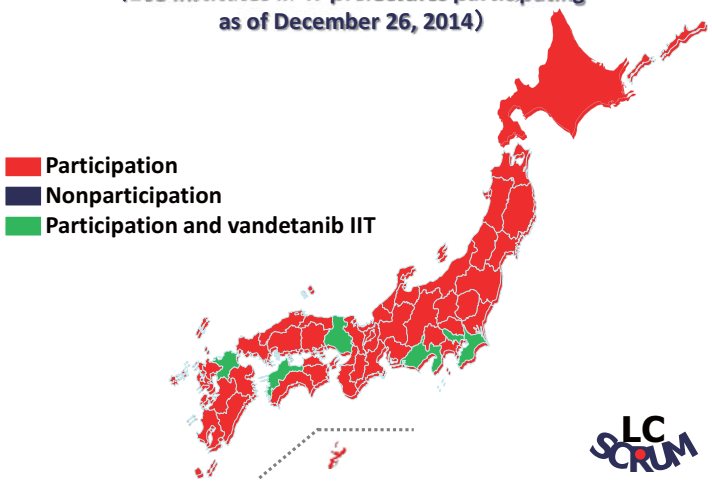
(58 institutes in 27 prefectures participating on January 19, 2013)



LC SCRUM

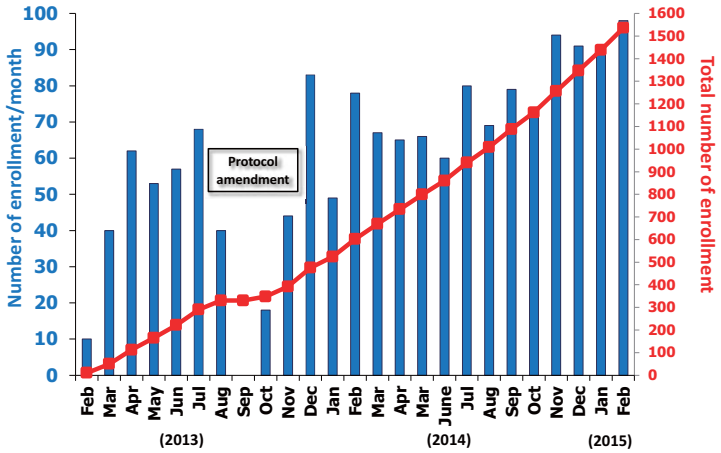
LC-SCRUM-Japan

（188 institutes in 47 prefectures participating as of December 26, 2014）



Patient enrollment in LC-SCRUM-Japan

A total of 1536 NSCLC patients were enrolled as of March 2015



Summary of Results

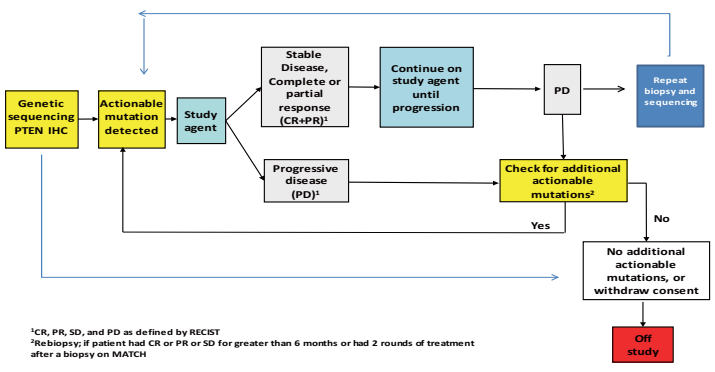
- A total of 1536 NSCLC patients were enrolled in LC-SCRUM-Japan.
- The success rate for RT-PCR and NGS analyses were 93% and 91%, respectively.
- *RET/ROS1/ALK* fusions were detected in 34 (2%)/61 (4%)/23 (2%) cases, respectively.
- The NGS analysis showed that 82 (41%) of the 201 *RET/ROS1/ALK* fusion-negative cases had driver mutations.
- The frequencies of *BRAF* and *ERBB2* mutations, 5% and 4%, respectively, were higher than those reported previously in NSCLCs.
- *MET/ERBB2/EGFR/FGFR1* amplifications were also detected by the NGS in 4 (2%)/2 (1%)/2 (1%)/1 (0.5%) cases, respectively.
- Among a total of 206 cases harboring targetable gene alterations, 19 with *RET* fusions, 26 with *ROS1* fusions, 3 with *ALK* fusions, 3 with *BRAF* mutations and 1 with an *ERBB2* mutation were enrolled in clinical trials of molecular targeted therapies

MULTI-ORGAN NATIONWIDE GENOME SCREENING; SCRUM-JAPAN

次世代分子生物学技術と情報技術を融合した「がん最適化医療」開発ネットワーク

米国のとりくみ：ゲノムマーカーによる大規模層別化臨床試験 “NCI-MATCH Trial”

SCHEMA



¹CR, PR, SD, and PD as defined by RECIST
²Rebiopsy; if patient had CR or PR or SD for greater than 6 months or had 2 rounds of treatment after a biopsy on MATCH

次世代分子生物学技術と情報技術を融合した「がん最適化医療」開発ネットワーク

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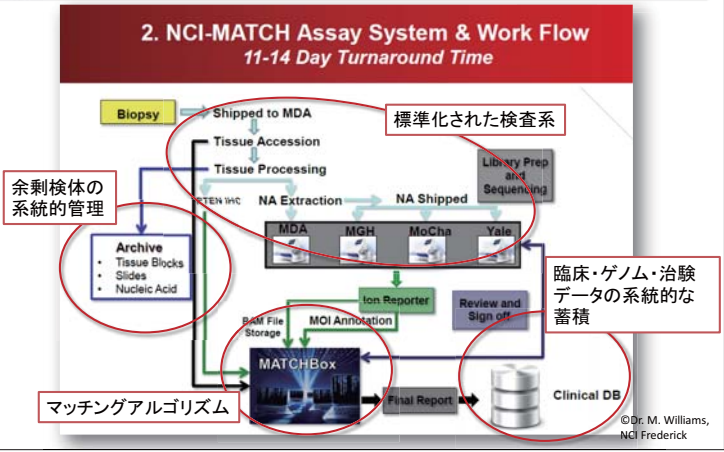
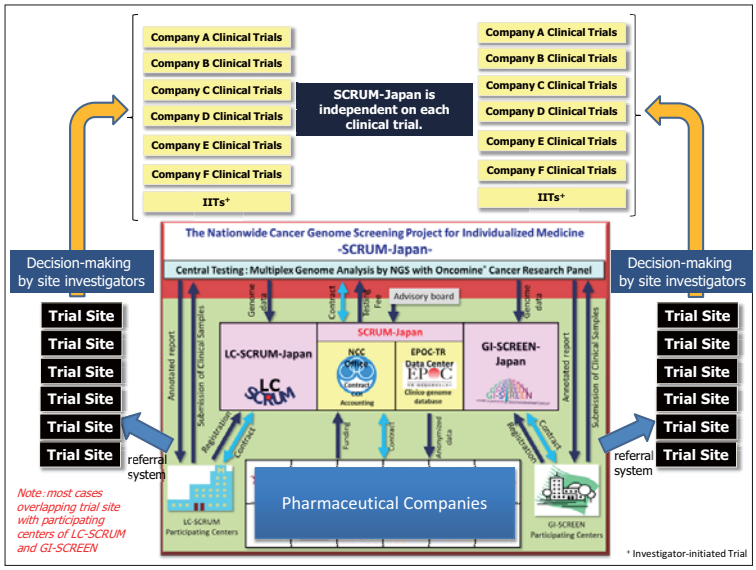
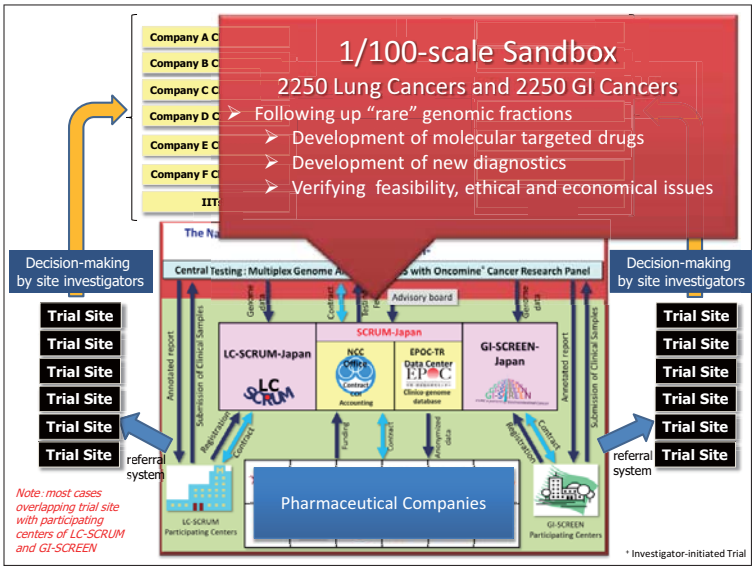
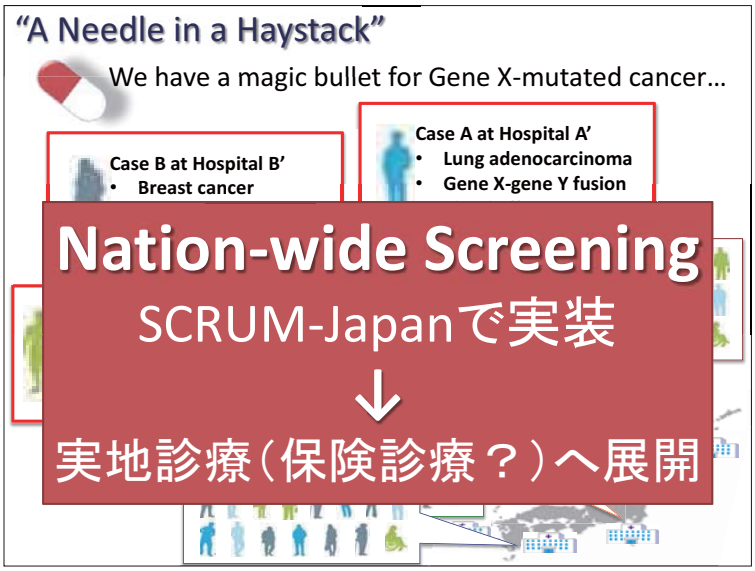



Company A Clinical Trials
Company B Clinical Trials
Company C Clinical Trials
Company D Clinical Trials
Company E Clinical Trials
Company F Clinical Trials
IITs*
SCRUM-Japan is independent on each clinical trial.
The Nationwide Cancer Genome Screening Project for Individualized Medicine -SCRUM-Japan-
Central Testing : Multiplex Genome Analysis by NGS with Oncomine™ Cancer Research Panel
Advisory board
SCRUM-Japan
LC-SCRUM-Japan
GI-SCREEN-Japan
Decision-making by site investigators
Trial Site
referral system
Pharmaceutical Companies
LC-SCRUM Participating Centers
GI-SCREEN Participating Centers
Note: most cases overlapping trial site with participating centers of LC-SCRUM and GI-SCREEN
* Investigator-initiated Trial


1/100-scale Sandbox
2250 Lung Cancers and 2250 GI Cancers
Following up “rare” genomic fractions
Development of molecular targeted drugs
Development of new diagnostics
Verifying feasibility, ethical and economical issues
Decision-making by site investigators
Trial Site
referral system
Pharmaceutical Companies
Note: most cases overlapping trial site with participating centers of LC-SCRUM and GI-SCREEN
* Investigator-initiated Trial


Actionable mutation に関連する治験情報の提供
http://epoc.ncc.go.jp/scrum/
LC-SCRUM-Japan 関連試験
GI-SCREEN-Japan 関連試験


“A Needle in a Haystack”
We have a magic bullet for Gene X-mutated cancer…
Case A at Hospital A’
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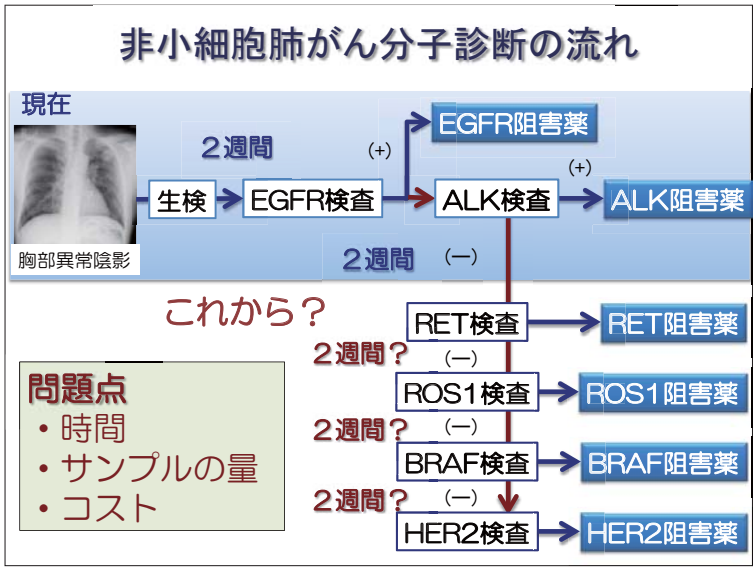
Breast cancer
Nation-wide Screening
SCRUM-Japanで実装
↓
実地診療（保険診療？）へ展開

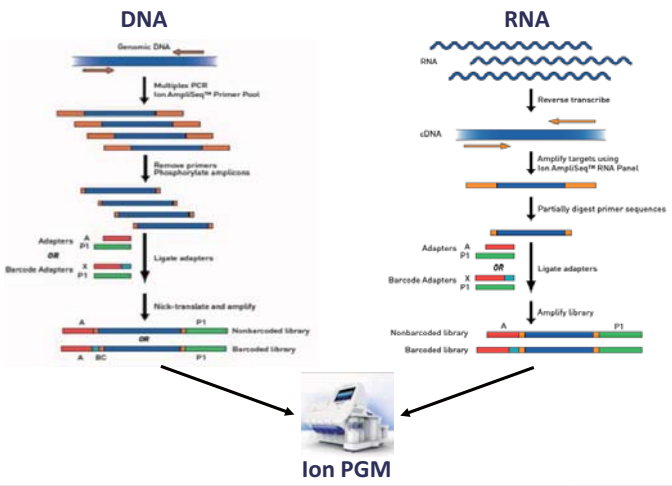

非小細胞肺がん分子診断の流れ
現在
胸部異常陰影
2週間
(+)
生検
EGFR検査
EGFR阻害薬
ALK検査
ALK阻害薬
2週間
(−)
これから？
RET検査
RET阻害薬
2週間？
ROS1検査
ROS1阻害薬
BRAF検査
BRAF阻害薬
HER2検査
HER2阻害薬
問題点
• 時間
• サンプルの量
• コスト

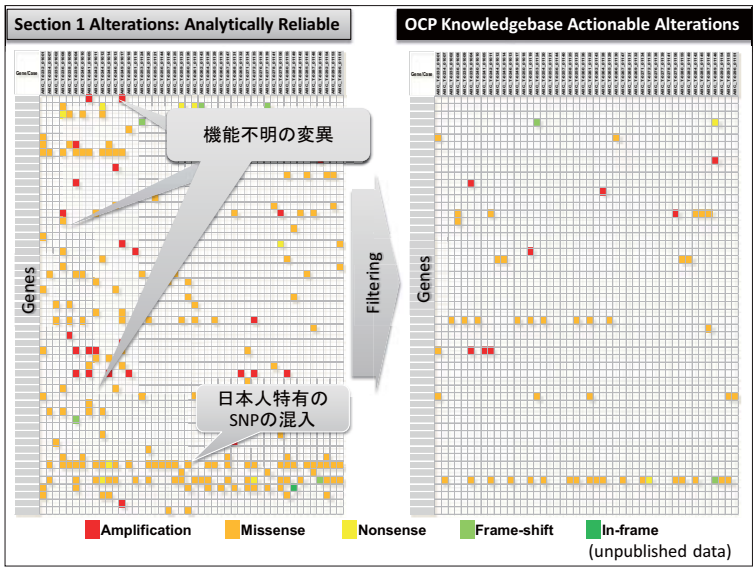

The Flood of Commercialized Clinical Cancer Sequencing
LDT
Laboratory developed test
解析法を開発した検査室でしか実施できない

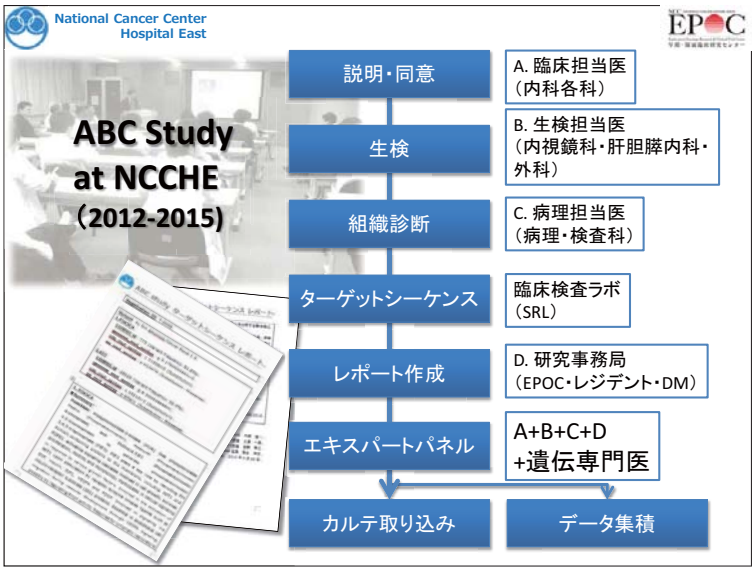
Oncomine® Cancer Research Panel Workflow

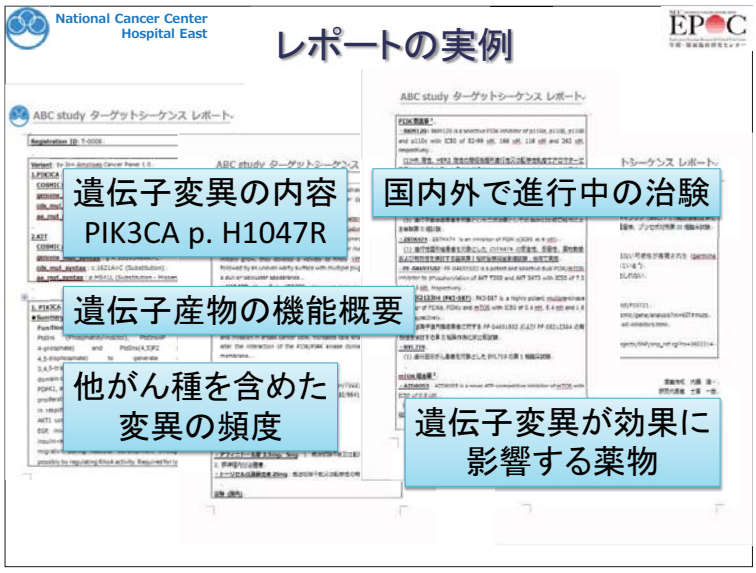
診断薬メーカーによるキットの品質保証
CLIA準拠ラボによる検査の品質管理
エビデンスに基づく報告様式の統一

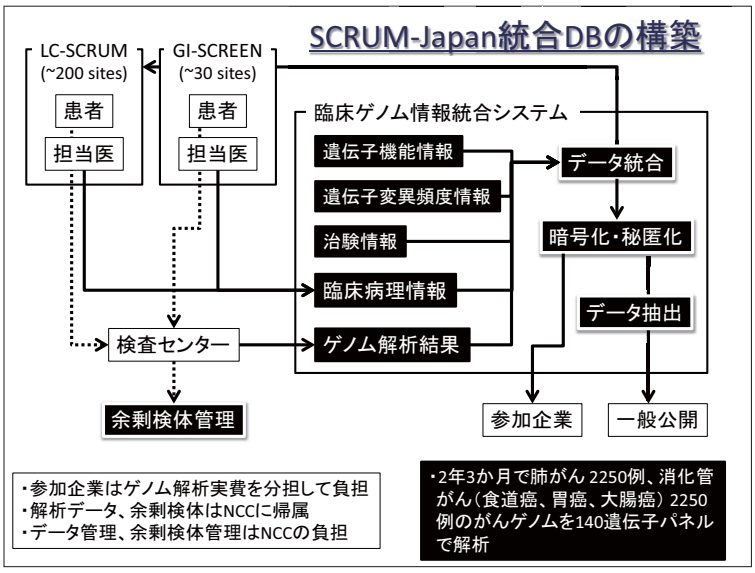
OCP143: Library Preparation

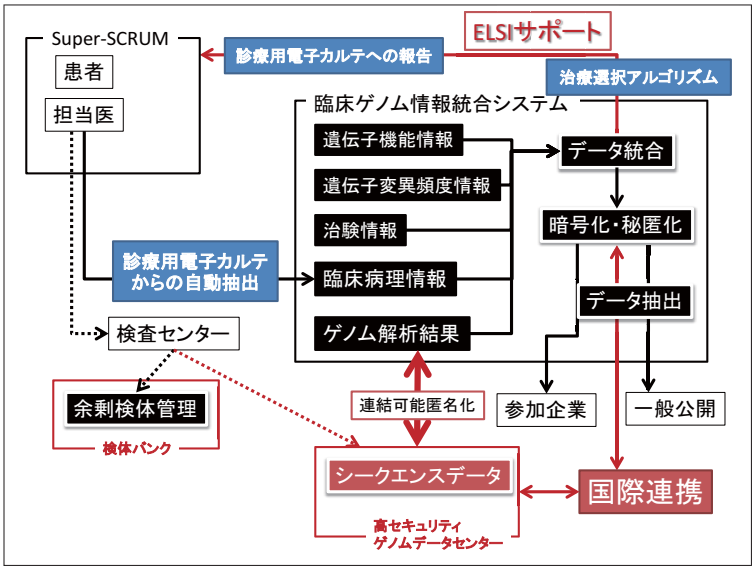


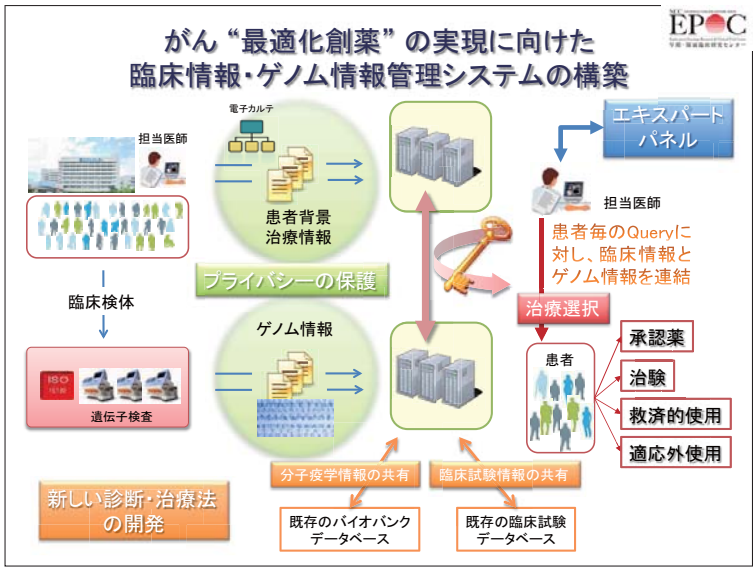


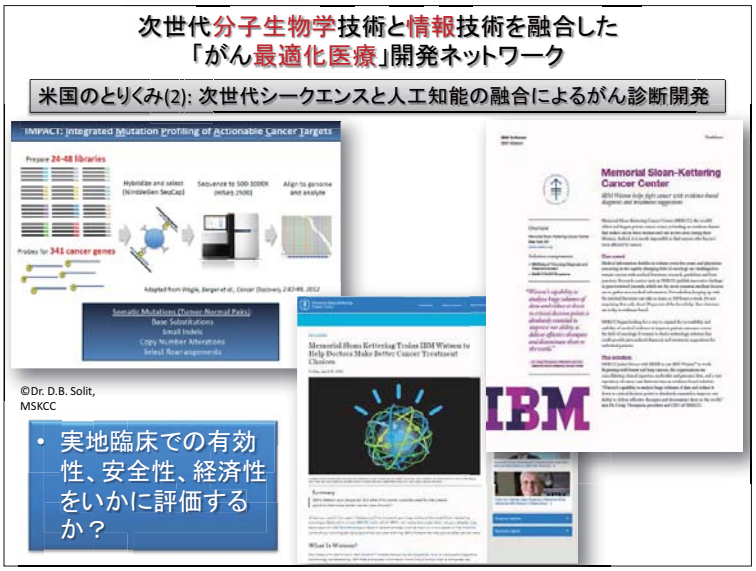












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Acknowledgement

SCRUM-Japan

- Participating institutes and companies
- Tomomitsu Hotta, Atsushi Ohtsu, Koichi Goto, Takayuki Yoshino, Genta Ohno (NCC)

National Cancer Center Hospital East

- Kiyotaka Yoh, Shigeki Umemura, Yoshitaka Zenke, Eri Sugiyama, Hibiki Udagawa, Yuki Matsumura (Fukushima Med Univ) , Tomohiro Miyoshi

NCCHE Office of Translational Research

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Dept. Computational Biology and Medical Sciences, The Univ. of Tokyo

- Yutaka Suzuki, Ken Matsui, , Toshihiko Maekawa, Minoru Kubota, Sumio Sugano,

Genomedia Inc.

- Yomoyuki Yamada, Koichiro Yamada