Precision Medicine and Molecular Tumor Board (MTB) Implementation in Oncology
癌症精準醫療與分子腫瘤委員會實踐

November 16, 2024

奇美醫院
蘇慧真

Precision Medicine in Oncology

- Precision oncology includes the integration of molecular tumor profiles into clinical decision-making in cancer treatment
- An increasing number of **molecularly guided treatment options** have received regulatory approval on the basis of genomic biomarkers for various tumor types
- **Next-generation sequencing (NGS)** started a new era of genetic testing, allowing specific tumor alterations to be matched with potential drugs, making these genetic mutations "druggable"
  - NGS allows sequencing of a high number of nucleotides in a short time frame

1. *Nat Med*. 2022 Apr;28(4):658-665.
2. *Tumori*. 2022 Aug;108(4):288-290.
3. *Ann Oncol.* 2020 Nov;31(11):1491-1505.

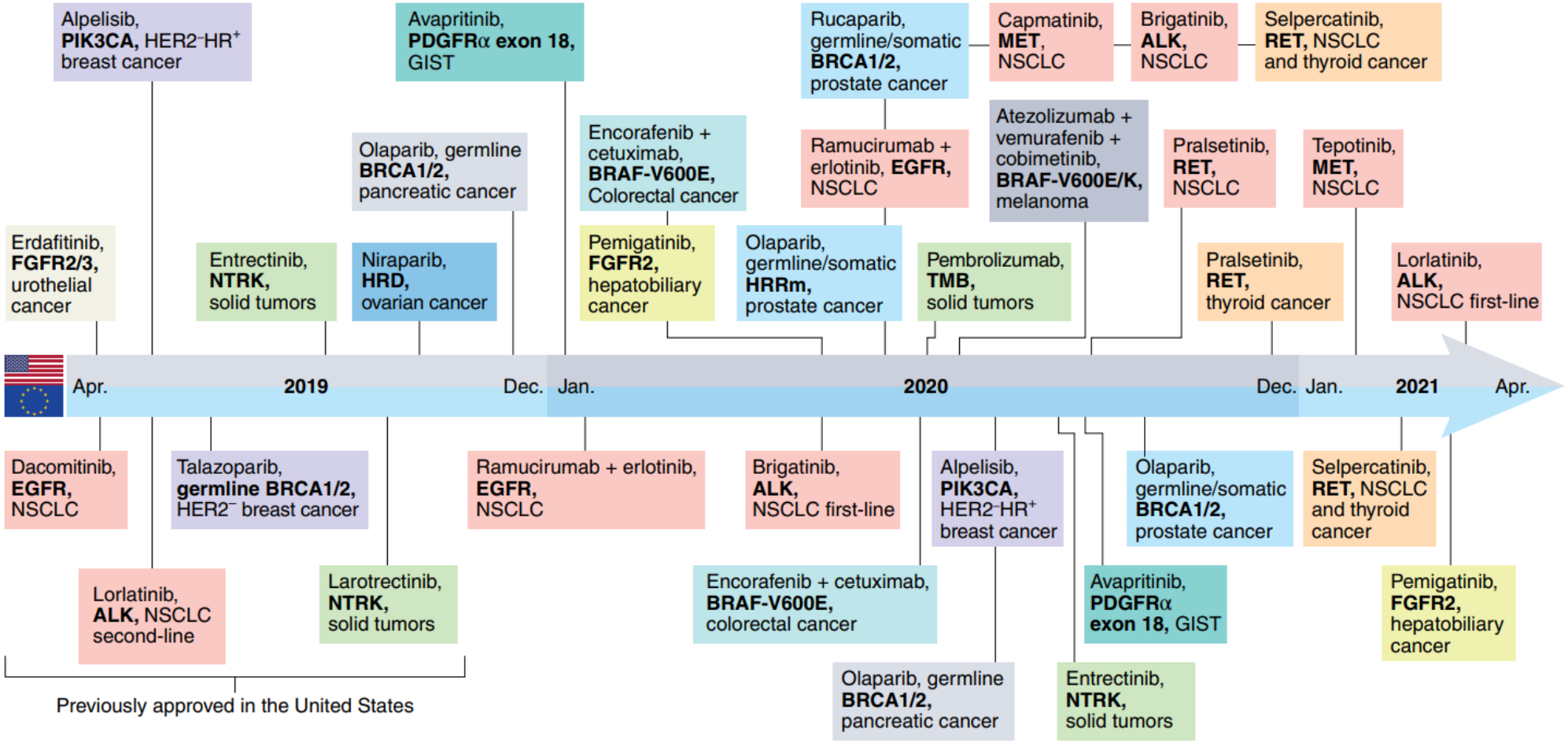
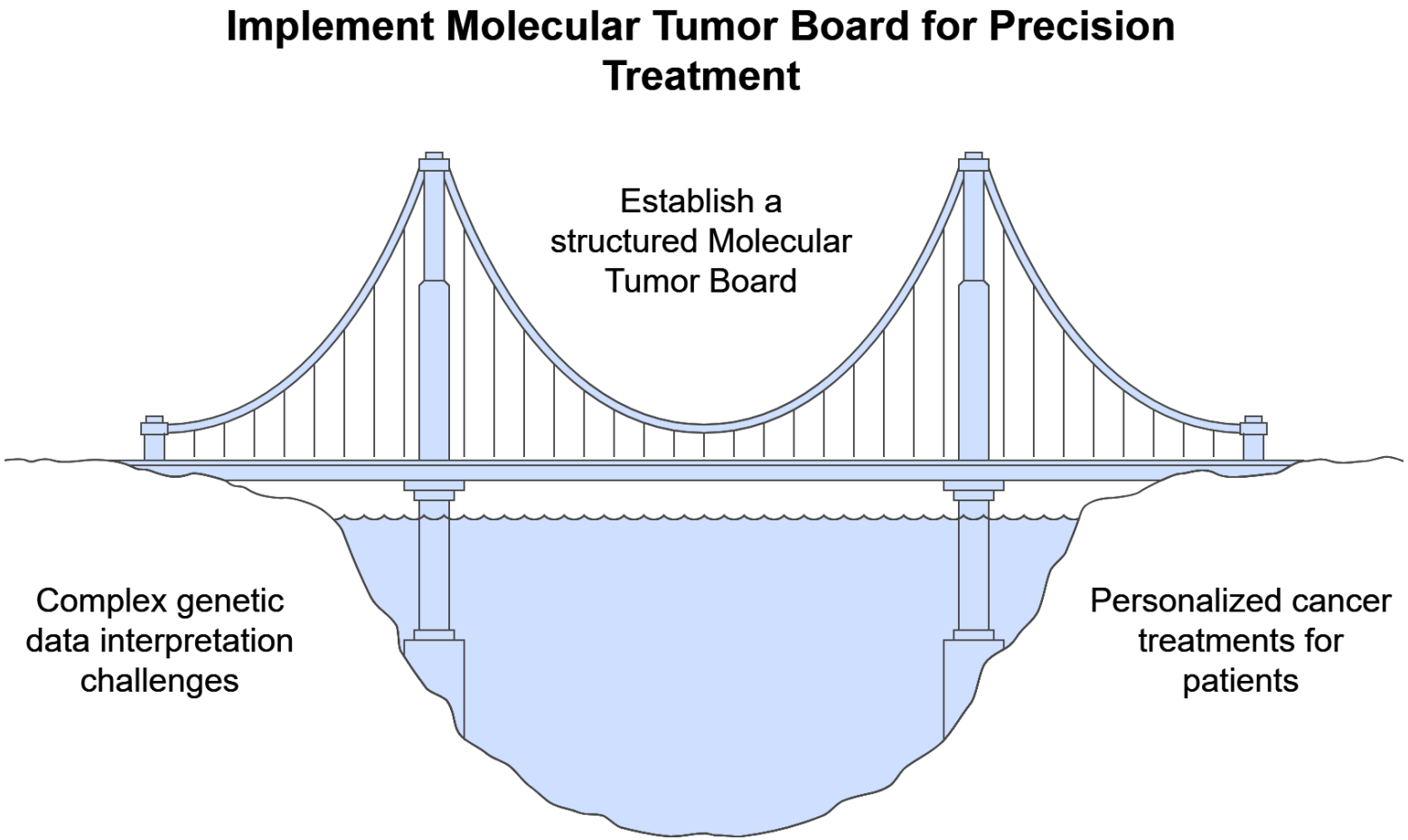


Fig. 1 | Genomic biomarker-driven drug approvals. Recent biomarker-specific solid tumor approvals relevant to comprehensive genomics profiling tests in the United States (Food and Drug Administration) (top half) and EU (EMA) (bottom half) between April 2019 and April 2021, as examples of the rapid advance in the number of available biomarker-driven treatment indications. Approvals related to other means of biomarker testing, such as immunohistochemistry assays, are not included. Each box includes a drug, the relevant biomarker (in bold), and the cancer type or disease setting for which the approval was granted by the relevant regulatory body. ALK, ALK receptor tyrosine kinase; GIST, gastrointestinal stromal tumor; EGFR, epidermal growth factor receptor; FGFR2/3, fibroblast growth factor receptor 2/3; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HRD, homologous recombination repair deficiency; HRRm, homologous recombination repair gene mutations; MET, MET proto-oncogene, receptor tyrosine kinase; NTRK, neurotrophic tyrosine receptor kinase; PDGFRα, platelet-derived growth factor alpha; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RET, Ret proto-oncogene; TMB, tumor mutational burden.

Nat Med. 2022 Apr;28(4):658-665.

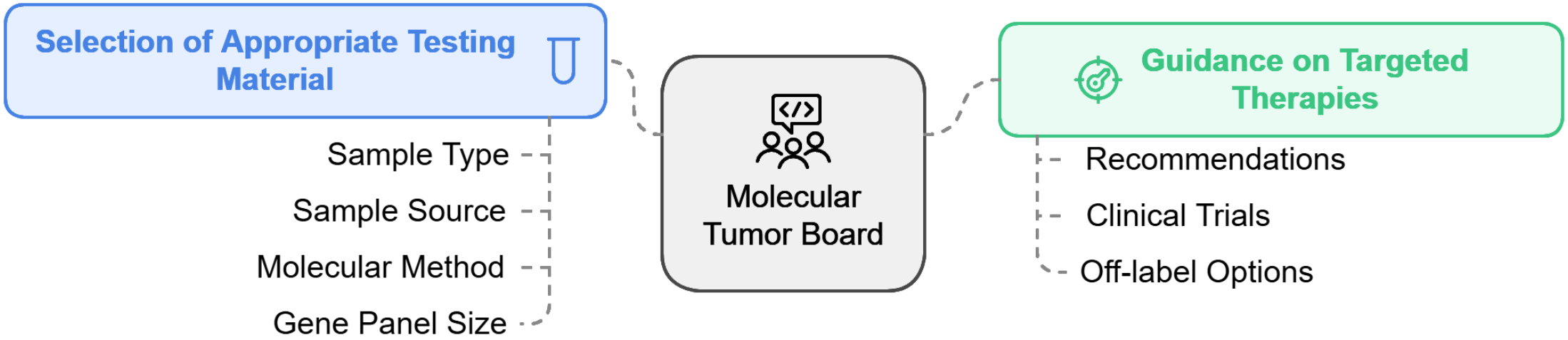
Rationale for Molecular Tumor Board (MTB) Implementation



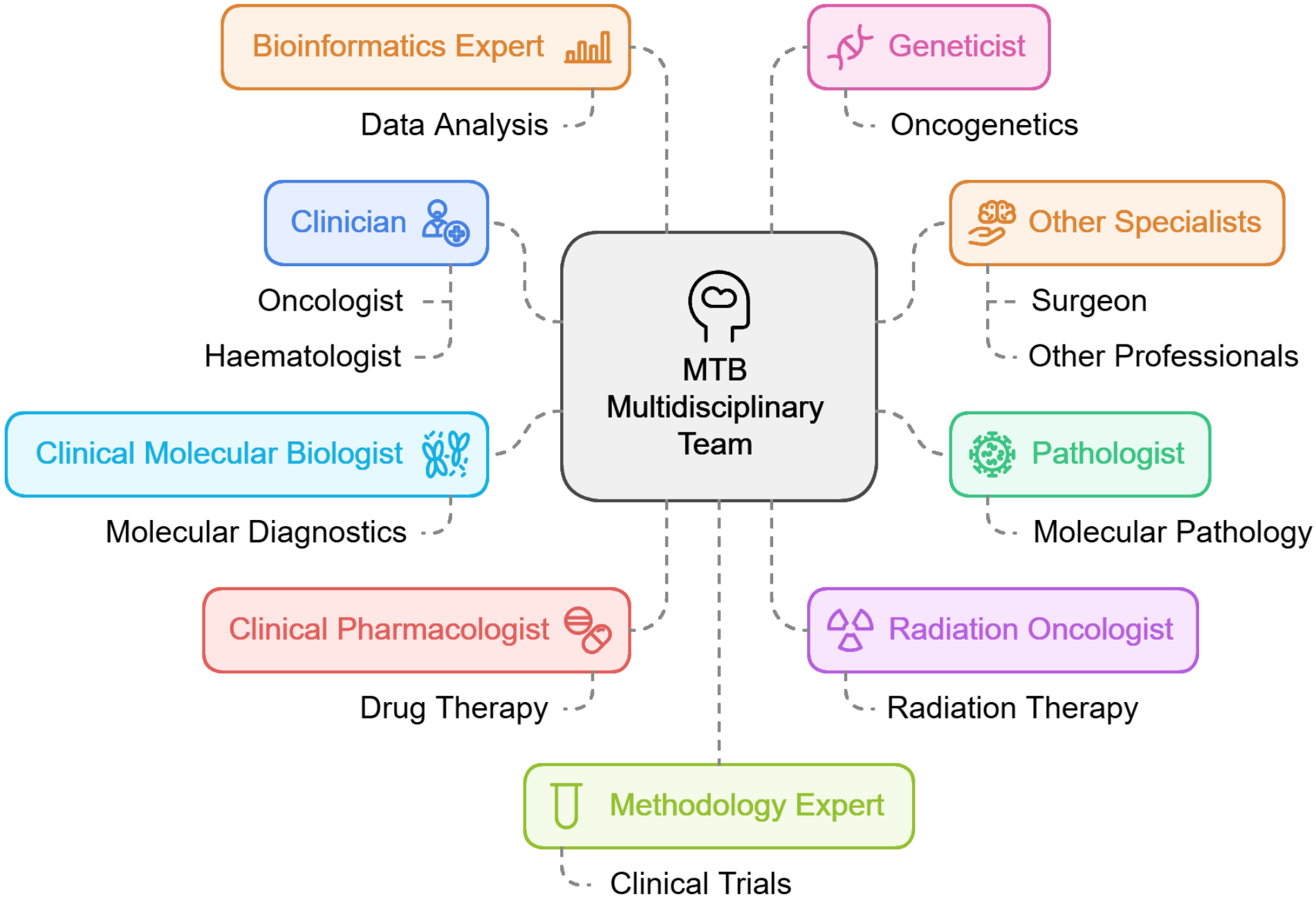
Tumori. 2022 Aug;108(4):288-290.

Aims of MTB

The general aim of MTB is to translate molecular data into information suitable by clinicians with prognostic and predictive indications



Crit Rev Oncol Hematol. 2022 Jan;169:103567.



Crit Rev Oncol Hematol. 2022 Jan;169:103567.

General Recommendations of the NGS for Daily Practice

- Tumor multigene NGS to assess alterations
  - **Lung adenocarcinoma**
  - **Prostate cancer**
  - **Cholangiocarcinoma**
  - **Ovarian cancers**: BRCA1/2
  - TMB (tumor mutational burden)
    - Cervical cancer, salivary cancer, thyroid cancers, well-to-moderately differentiated neuroendocrine tumors, vulvar cancer
- No current indication for tumor multigene NGS
  - Squamous cell lung cancers
  - Breast cancers
  - Gastric cancers
  - Hepatocellular carcinoma
- Use of Large Panels: Larger gene panels can be used based on specific agreements with payers, especially if they provide cost-effectiveness and accurate alteration ranking

Ann Oncol. 2020 Nov;31(11):1491-1505.

Other Recommendations of the NGS

- Clinical research centers are encouraged to conduct multigene sequencing as part of molecular screening programs
  - This can increase access to new drugs and speed up clinical research, especially in cases where level II-IV* alterations are frequent (e.g., breast, pancreatic, and hepatocellular cancers)
- Patient-Centric Considerations
  - NGS may be used with large gene panels in specific patient-doctor decisions if there is no additional cost burden on public health, and if patients are informed about the potential low likelihood of benefit

*Level of ESCAT (The ESMO Scale for Clinical Actionability of molecular Targets):

- ESCAT level I means that the match of an alteration and a drug has been validated in clinical trials, and should drive treatment decision in daily practice.
- ESCAT level II means that a drug that matches the alteration has been associated with responses in phase I/ II or in retrospective analyses of randomized trials.
- ESCAT level III includes alterations that are validated in another cancer, but not in the disease-to-treat.
- ESCAT level IV includes hypothetically targetable alterations based on preclinical data.

Ann Oncol. 2020 Nov;31(11):1491-1505.

Table 3A. List of genomic alterations level I/II/III according to ESCAT in advanced non-squamous non-small-cell lung cancer (NSCLC)

Gene	Alteration	Prevalence	ESCAT	References
EGFR	Common mutations (*Del19, L858R*)	15% (50%–60% Asian)	IA	Midha A, et al. *Am J Cancer Res.* 2015[26]
	Acquired *T790M* exon 20	60% of *EGFR* mutant	IA	Mok T, et al. *J Clin Oncol.* 2018[27]
	Uncommon *EGFR* mutations (*G719X* in exon	NSCLC	IB	Soria J-C, et al. *N Engl J Med.* 2018[28]
	18, *L861Q* in exon 21, *S768I* in exon 20)	10%	IIB	Ramalingam S, et al. *N Engl J Med.* 2020[29]
	Exon 20 insertions	2%		Mok T, et al. *N Engl J Med.* 2017[30]
				Yang JC-H, et al. *Lancet Oncol.* 2015[31]
				Cho J, et al. *J Thorac Oncol.* 2018[32]
				Cardona A, et al. *Lung Cancer.* 2018[33]
				Heymach J, et al. *J Thorac Oncol.* 2018[34]
ALK	Fusions (mutations as mechanism of resistance)	5%	IA	Solomon B, et al. *J Clin Oncol.* 2018[35]
				Soria J-C, et al. *Lancet.* 2017[36]
				Peters S, et al. *N Engl J Med.* 2017[37]
				Zhou C, et al. *Ann Oncol.* 2018[38]
				Camidge D, et al. *N Engl J Med.* 2018[39]
MET	Mutations *ex 14 skipping*	3%	IB	Tong J, et al. *Clin Cancer Res.* 2016[40]
				Drilon A, et al. *Nat Med.* 2020[41]
	Focal amplifications (acquired resistance on EGFR TKI in *EGFR*-mutant tumours)	3%	IIB	Camidge D, et al. *J Clin Oncol.* 2018[52]
BRAF^{V600E}	Mutations	2%	IB	Planchard D, et al. *Lancet Oncol.* 2016[42]
				Planchard D, et al. *Lancet Oncol.* 2017[43]
				Planchard D, et al. *J Clin Oncol.* 2017[44]
ROS1	Fusions (mutations as mechanism of resistance)	1%–2%	IB	Shaw A, et al. *N Engl J Med.* 2014[45]
				Shaw A, et al. *Ann Oncol.* 2019[46]
				Drilon A, et al. *Lancet Oncol.* 2020[47]
NTRK	Fusions	0.23%–3%	IC	Drilon A, et al. *N Engl J Med.* 2018[48]
				Hong D, et al. *Lancet Oncol.* 2020[49]
				Doebele RC, et al. *Lancet Oncol.* 2020[50]
RET	Fusions	1%–2%	IC	Drilon A, et. *J Thorac Oncol.* 2019[51]
KRAS^{G12C}	Mutations	12%	IIB	Barlesi F, et al. *Lancet.* 2016[53]
				Fakih M, et al. *J Clin Oncol.* 2019[54]
ERBB2	Hotspot mutations	2%–5%	IIB	Hyman D, et al. *Nature.* 2018[55]
	Amplifications			Wang Y, et al. *Ann Oncol.* 2018[56]
				Tsurutani J, et al. *J Thorac Oncol.* 2018[57]
BRCA 1/2	Mutations	1.2%	IIIA	Balasubramaniam S, et al. *Clin Cancer Res.* 2017[63]
PIK3CA	Hotspot mutations	1.2%–7%	IIIA	Cancer Genome Atlas Research Network. *Nature.* 2014[60]
				Vansteenkiste J, et al. *J Thorac Oncol.* 2015[62]
NRG1	Fusions	1.7%	IIIB	Duruisseaux M, et al. *J Clin Oncol.* 2019[59]

Criteria for the Selection of Patients to Be Evaluated by the MTB

- Despite the ever-expanding need for the MTB empowerment in clinical oncology practice, no standard guidelines exist to address the workflow
- MTB case discussions are particularly valuable for patients with
  - Rare mutations
  - Gene alterations not associated with known drug response or resistance
  - Rare tumors without available treatment options
  - “Oncogene-addicted” tumors unresponsive to existing targeted therapies
- Inclusivity of Case Discussion Across All Tumor Types
  - All types of neoplasms, regardless of sample type (cytological or histological), can be discussed within MTBs for potential molecular analysis and therapeutic consideration

Crit Rev Oncol Hematol. 2022 Jan;169:103567.

Workflow for Genomic Profiling and Treatment Recommendations

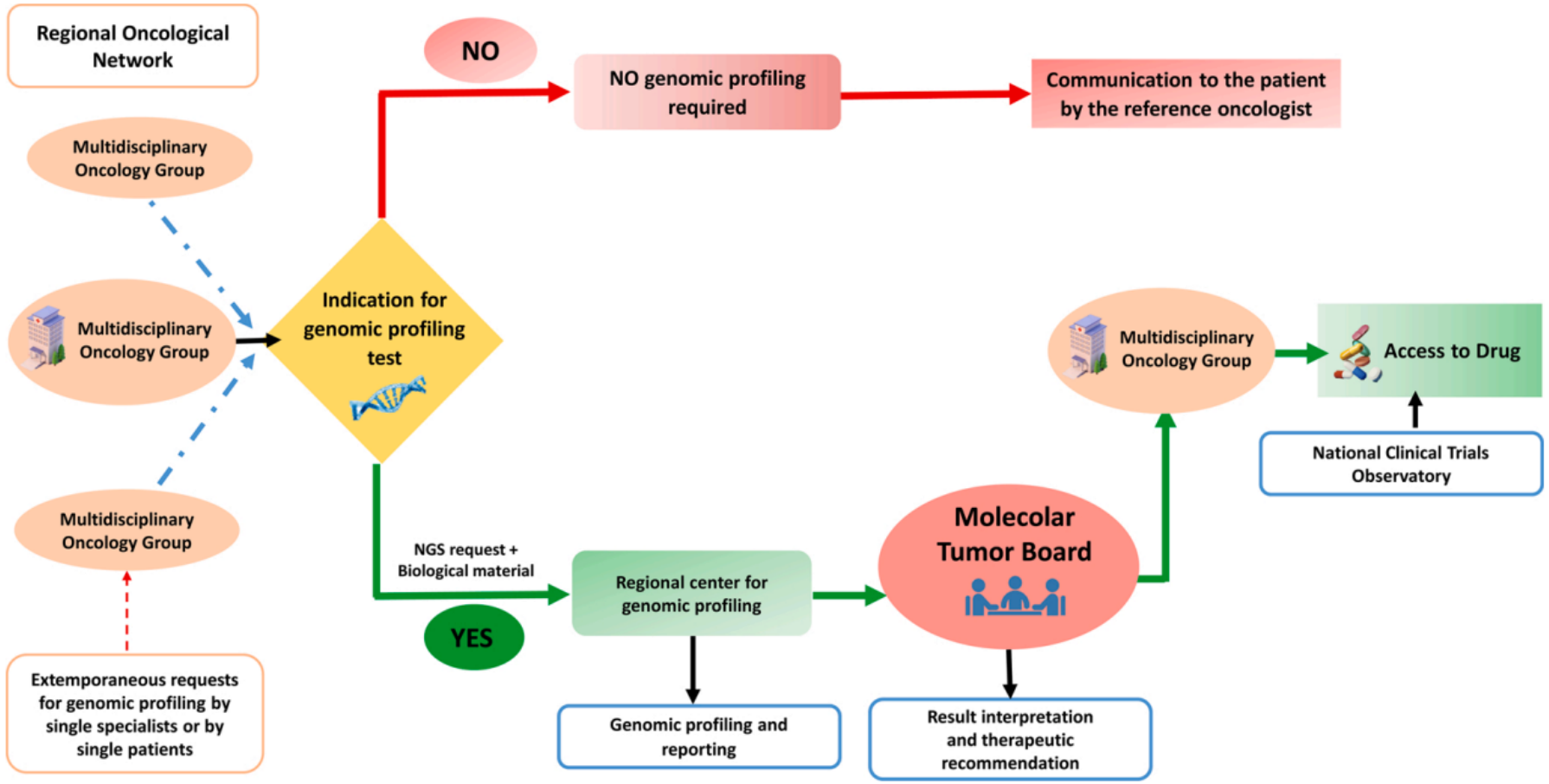


Fig. 1. The critical step from the Multidisciplinary Oncology Group to Molecular Tumor Board consultation and patient's treatment recommendation.

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健保2024年5月1日起給付癌症精準醫療「實體癌/血癌次世代基因定序檢測(NGS)」

- 給付對象
  - 實體腫瘤：包括14種癌別，9種[a]適用NGS(非小細胞肺癌、三陰性乳癌等)，5種[b]癌別則採單基因檢測
  - 血液腫瘤：急性骨髓性白血病(AML)、高風險之骨髓分化不良症狀群(MDS)、急性淋巴芽細胞白血病(B-ALL及T-ALL)、B細胞淋巴癌(BCL)、T或NK細胞血癌與淋巴癌(NKTL)
- 給付內容
  - BRCA基因檢測1萬點、小套組(≦100基因)2萬點、大套組(>100基因)3萬點
- 檢測規範
  - 每癌別患者終生僅可給付一次。檢測須在區域級以上或癌症認證醫院進行，由衛福部核定的核定之實驗室開發檢測機構施行，**並須自行設立或跨院聯合組成分子腫瘤委員會(MTB)**以強化臨床跨領域合作

[a]非小細胞肺癌、三陰性乳癌、卵巢癌/輸卵管癌/原發性腹膜癌、攝護腺癌、胰臟癌、NTRK基因融合實體腫瘤、肝內膽管癌、甲狀腺癌、甲狀腺髓質癌
[b]大腸直腸癌、泌尿道上皮癌、黑色素瘤、腸胃道間質瘤及胃癌

https://www.nhi.gov.tw/ch/cp-14565-e02e0-3255-1.html

奇美醫院精準醫療簡介與沿革

- 奇美醫學中心為因應精準醫療的浪潮，統合規劃體系內檢驗量能，以及聚焦臨床需求，於2021年10月1日成立「精準醫學中心」
- 由醫療副院長田宇峯出任中心主任，下轄精準醫學核心實驗室及跨專科組成的臨床精準醫學團隊，共同推動精準醫學醫療業務

https://www.chimei.org.tw/main/cmh_department/59012/magazin/vol135/03-1.html

奇美醫院精準醫療簡介與沿革

- 與臺灣名列前茅的基因檢測公司「行動基因」合作技術轉移次世代定序領域
  - 透過技術轉移合作，縮短次世代基因定序領域的學習曲線，增進大數據處理能力
  - 癌症次世代定序基因檢測正式於奇美醫學中心上線
- 2022年7月開設「癌症基因檢測諮詢門診」
- 2024年1月25日成立「分子腫瘤委員會」

奇美醫院精準醫學中心
Center For Precision Medicine, Chi Mei Medical Center

ACT GENOMICS 行動基因
Turn Genomics into Action

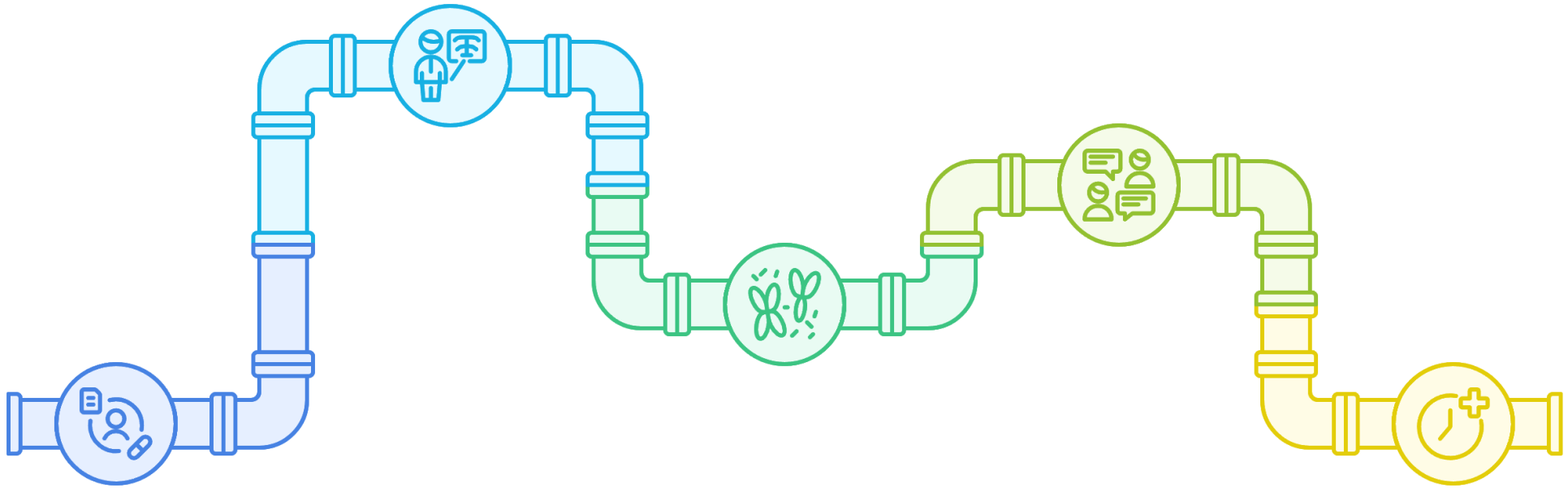
https://www.chimei.org.tw/main/cmh_department/59012/magazin/vol135/03-1.html

奇美醫院分子腫瘤委員會簡介

- 組織架構
  - 設主任委員及副主任委員各一人
  - 設總幹事一人，協助處理委員會之相關事務
  - 本委員會為跨院區委員會
    - 委員會成員：總院精準醫學中心、血液腫瘤科、藥劑部與柳營院區血液腫瘤科及院外專家代表
    - 列席委員：總院癌症中心、柳營院區癌症中心、總院臨床試驗中心、柳營院區臨床試驗中心
- 開會頻率：本會每月定期召開會議一次 (每月第二週；週三12：00~13：30)
- 會議討論提報機制與討論重點
  - 由各癌症多專科醫療團隊醫師自行提報，討論時機可為治療前或治療後
  - **會議須著重針對基因檢測結果，提供主治醫師諮詢、用藥、診療建議及治療效果評估討論**
  - 討論案例若需其他院外臨床或基礎研究專家參與提供意見，得依討論個案逐案提出邀請

奇美醫療財團法人奇美醫院分子腫瘤委員會組織章程

奇美醫院分子腫瘤委員會案例討論流程



01

案例提報

主治醫師在會議前一周提報預計討論案例給總幹事

02

案例介紹

提報主治醫師簡介案例背景及治療過程

03

專家分析

病理學和基因專家分析報告

04

委員會討論

委員會成員討論可行的治療方案提出意見

05

最終治療建議記錄

記錄並確認最終的治療建議

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王業翰 (來賓) (未驗證)

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癌

癌症中心_周宇玲

癌症中心_吳怡佳

奇美總院 (來賓) (未驗證)

編

編制外計畫人員_莊惠嫚

癌

癌症中心_吳佩樺

李

李宛珊 (來賓) (未驗證)

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敏家個管師 (來賓) (未驗證)

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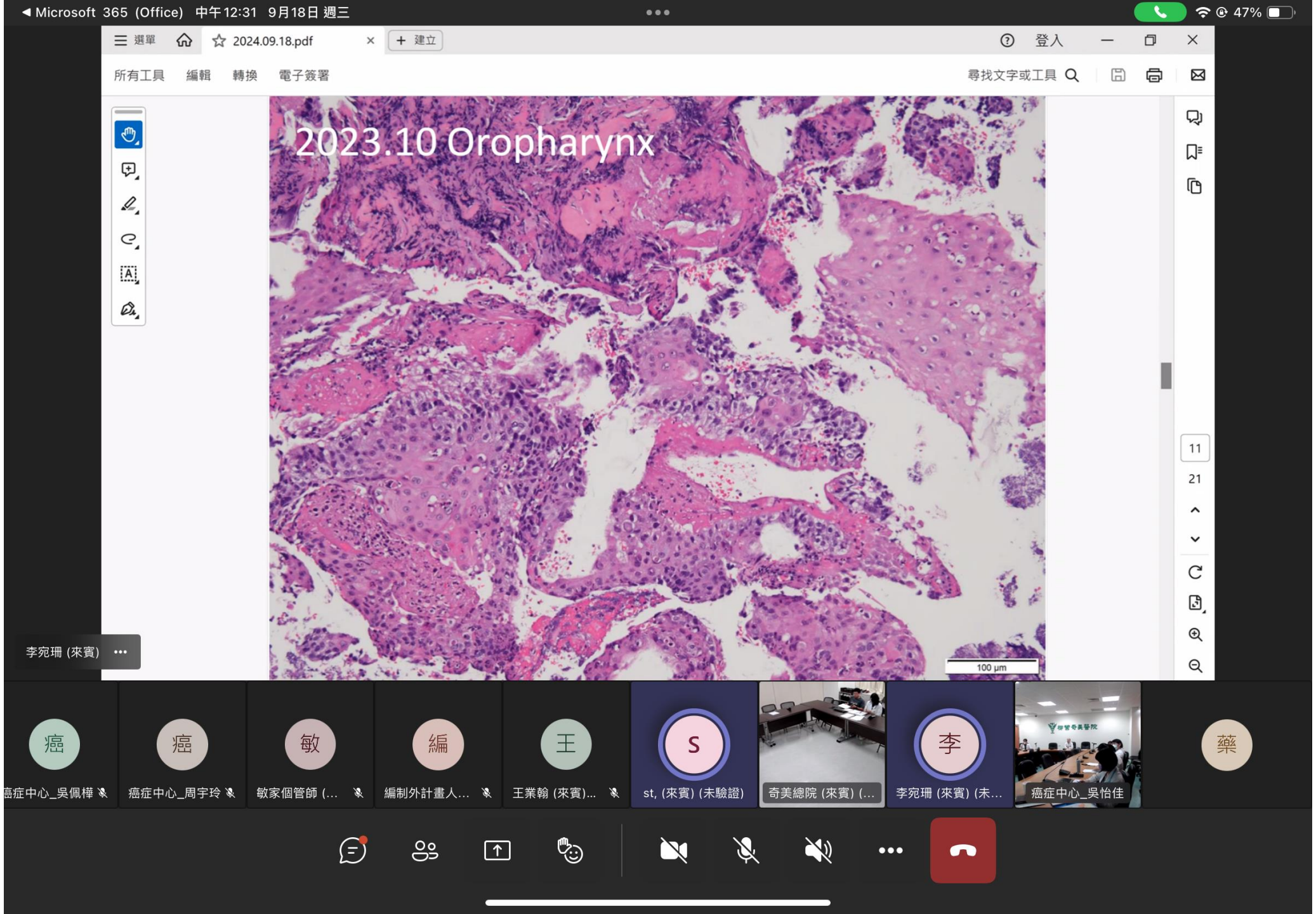
分子病理科_李宛珊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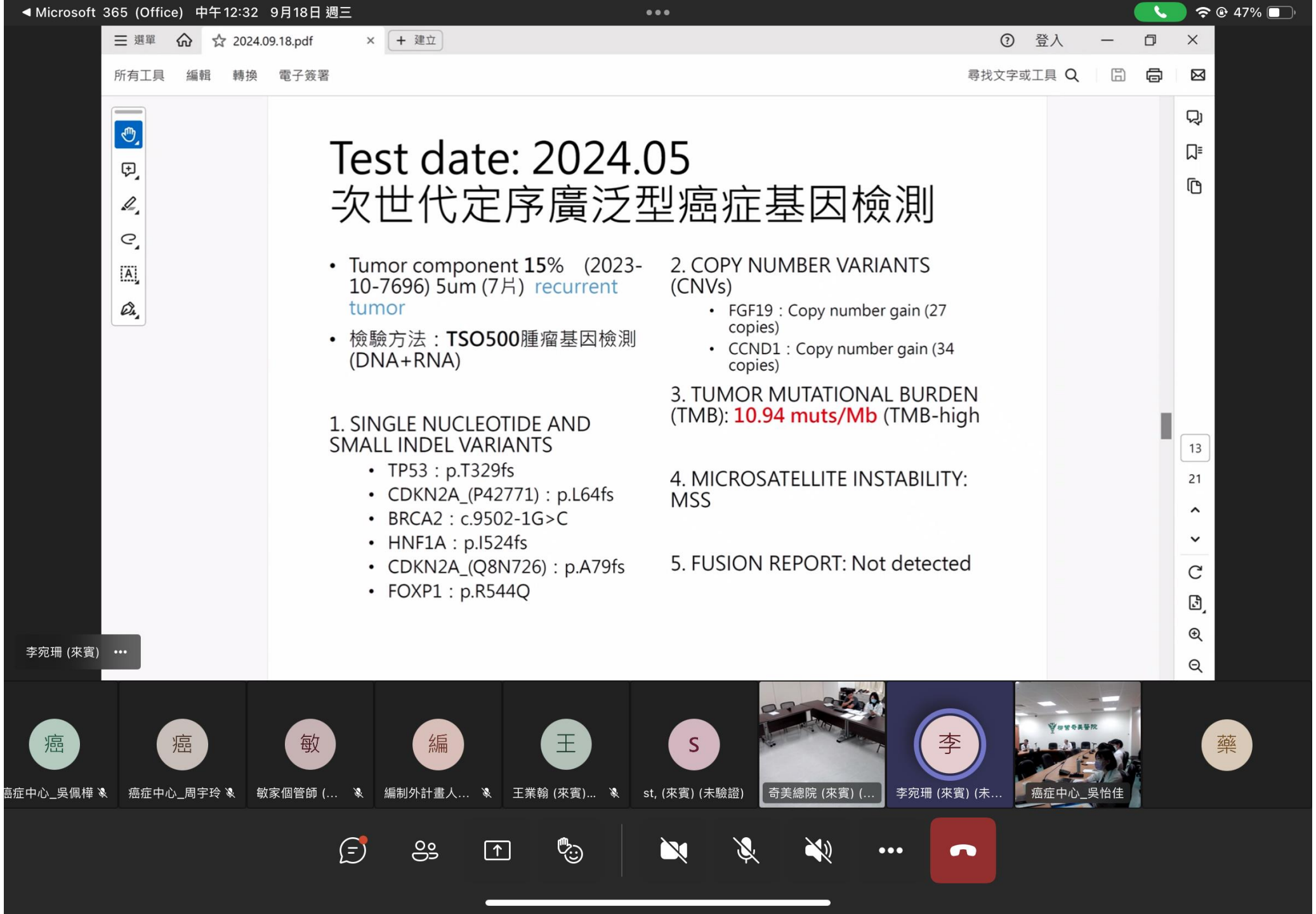
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Test date: 2024.05
次世代定序廣泛型癌症基因檢測
• Tumor component 15% (2023-10-7696) 5um (7片) recurrent tumor
• 檢驗方法：TSO500腫瘤基因檢測 (DNA+RNA)
1. SINGLE NUCLEOTIDE AND SMALL INDEL VARIANTS
• TP53：p.T329fs
• CDKN2A_(P42771)：p.L64fs
• BRCA2：c.9502-1G>C
• HNF1A：p.I524fs
• CDKN2A_(Q8N726)：p.A79fs
• FOXP1：p.R544Q
2. COPY NUMBER VARIANTS (CNVs)
• FGF19：Copy number gain (27 copies)
• CCND1：Copy number gain (34 copies)
3. TUMOR MUTATIONAL BURDEN (TMB): 10.94 muts/Mb (TMB-high
4. MICROSATELLITE INSTABILITY: MSS
5. FUSION REPORT: Not detected
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李宛珊 (來賓)
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癌症中心_周宇玲
敏家個管師 (...
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Different ALK TKIs may lead to different ALK mutation

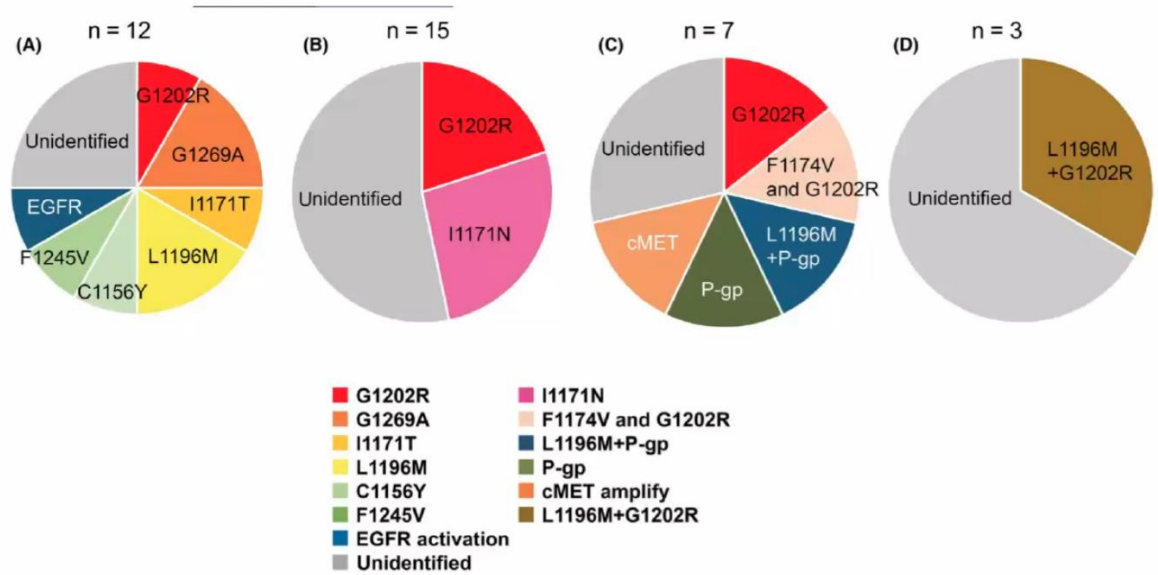

FIGURE 2 Overview of the on-target mechanisms of resistance among patients with anaplastic lymphoma kinase-positive specimens. Analysis of specimens obtained from patients who presented with disease progression after treatment with (A) crizotinib, (B) alectinib, (C) ceritinib and (D) lorlatinib

7

王業翰 (來賓) •••

癌症中心_吳佩樺 | 癌症中心_周宇玲 | 敏家個管師 (... | 編制外計畫人... | 李宛珊 (來賓) (未... | st, (來賓) (未驗證) | 王業翰 (來賓) (未... | 奇美總院 (來賓) (... | 癌症中心_吳怡佳


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奇美醫療財團法人 柳營奇美醫院
Chi Mei Hospital, Liouying
針對確定性局部區域治療IB-IIIA期RET融合-非小細胞肺癌(NSCLC)陽性參與者後之Selpercatinib輔助治療的一項安慰劑對照、雙盲、第3期隨機分配試驗
收案重點
1.stage Ib~IIIA
2.可在手術前送Liquid NGS(optional)手術後送slide NGS
3.一定要可執行治癒性手術
PI:
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癌症中心_吳怡佳
癌症中心_吳佩樺
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分子腫瘤委員會個案討論記錄單

Molecular Tumor Board Report

姓名：_____☐男☐女

病歷號：_____

生日：_____/_____/_____

會議日期：　　年　　月　　日、時間：　　點　　分至　　點　　分

參加科別：☐血液腫瘤科☐分子病理科☐精準醫學中心☐藥劑部☐癌症中心☐臨床試驗中心☐其他：_____

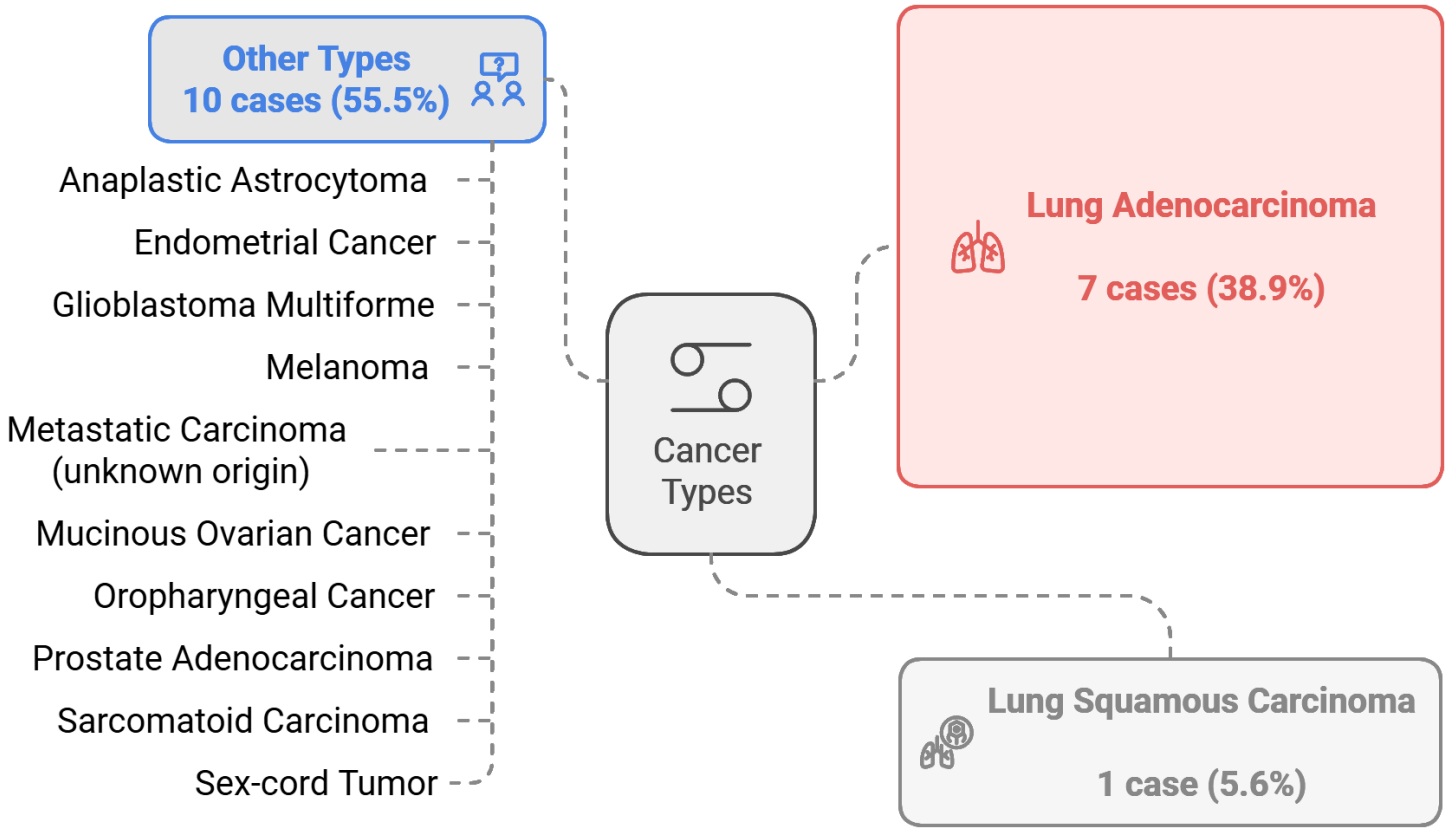
診　　斷：_____

期　　別：_____

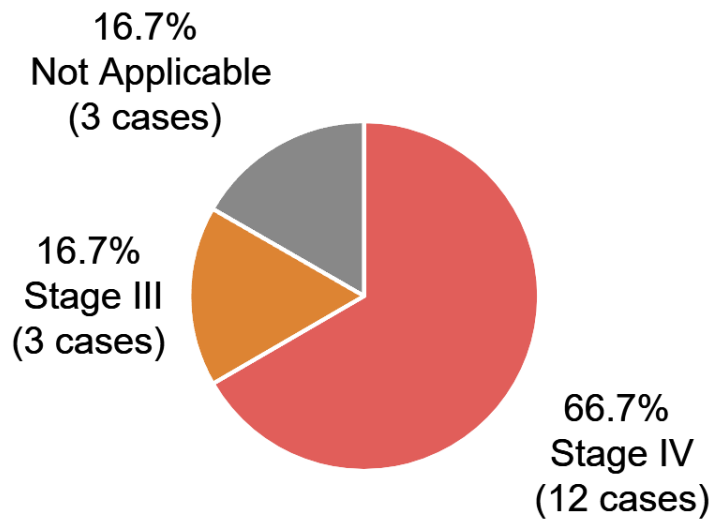
Sample information	
Type of sample	☐ Tumor tissue primary ☐ Tumor tissue metastasis ☐ Plasma sample for circulating tumor DNA ☐ Tumor tissue and germline ☐ Other:
Platform	
Tumor cellularity (Tissue) / Tumor fraction (Liquid)	
Quality of concern	☐ Aged tissue ☐ Low tumor cellularity ☐ Others: ☐ NA
Time of NGS	☐ At diagnosis ☐ Before systemic therapy ☐ After the failure of standard therapies ☐ After curative therapy
Actionable genetic alterations	

CMH MTB Experience Sharing (from Apr 2024 to Oct 2024)

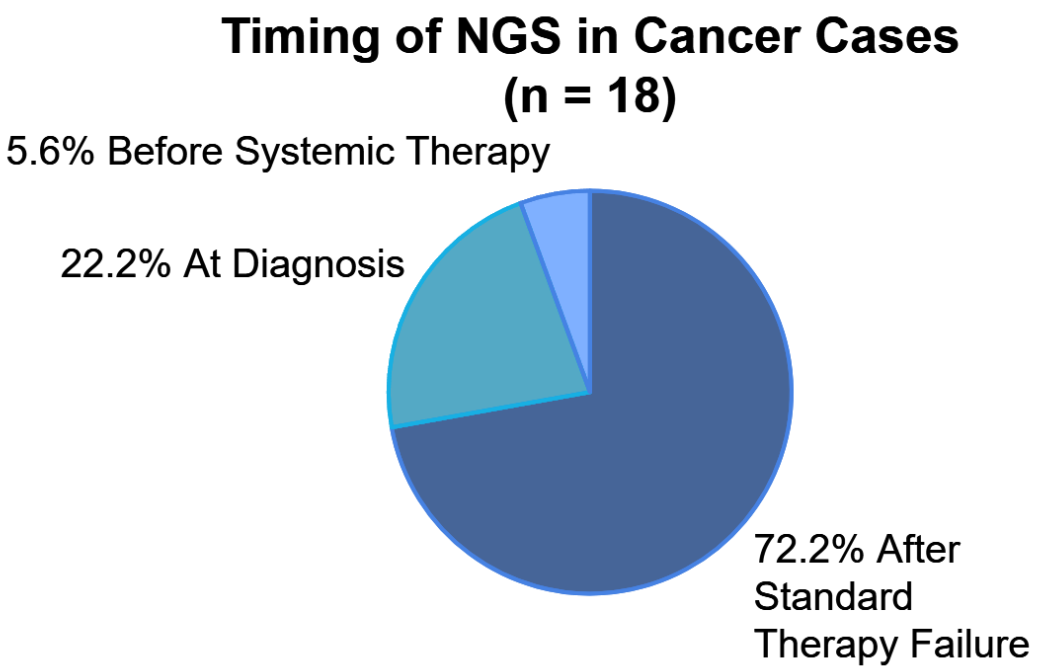
Distribution of Cancer Types (n = 18)

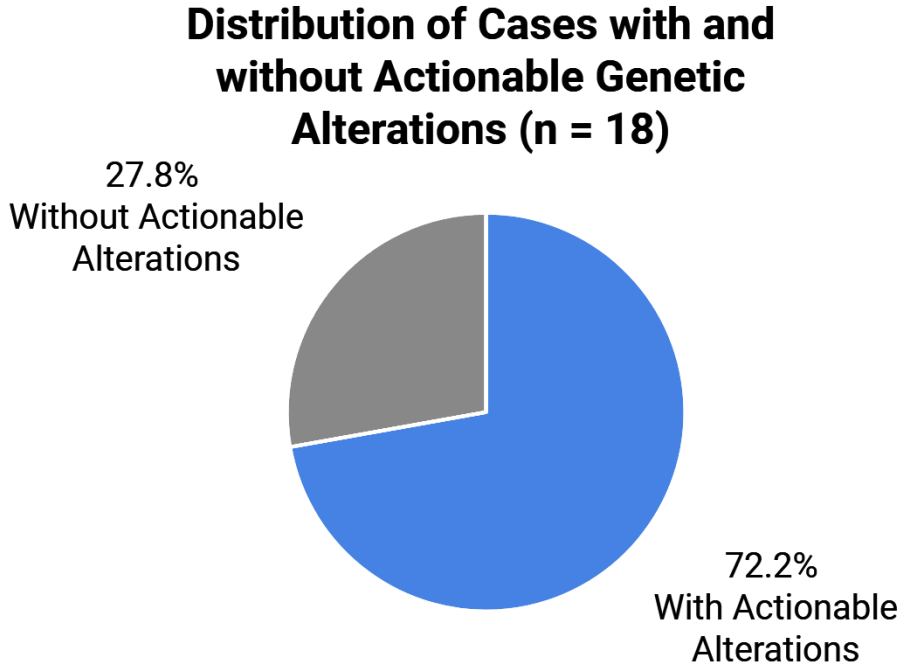


Distribution of Cases by Stage (n = 18)



CMH MTB Experience Sharing (from Apr 2024 to Oct 2024)





CMH MTB Experience Sharing (from Apr 2024 to Oct 2024)

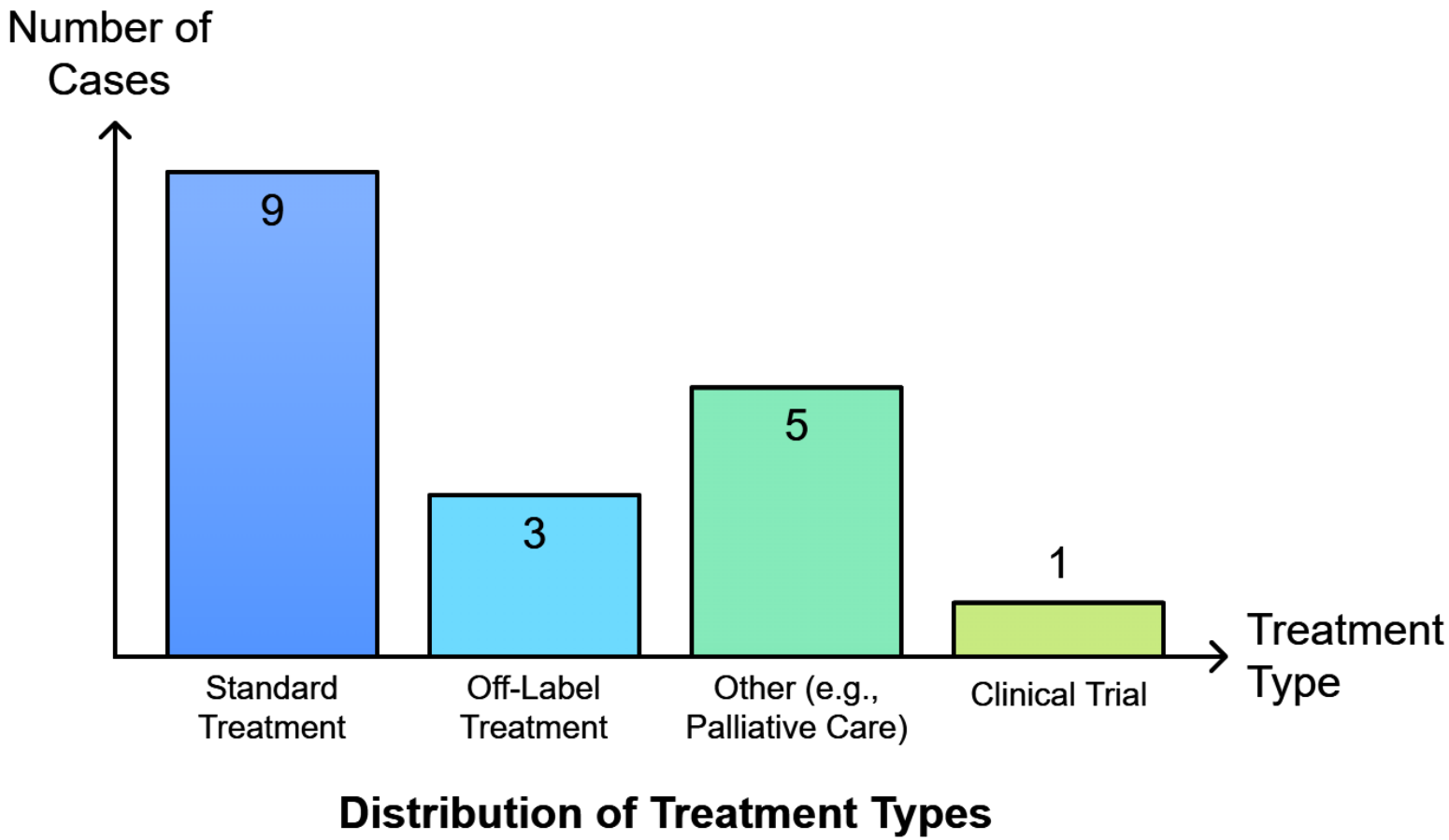


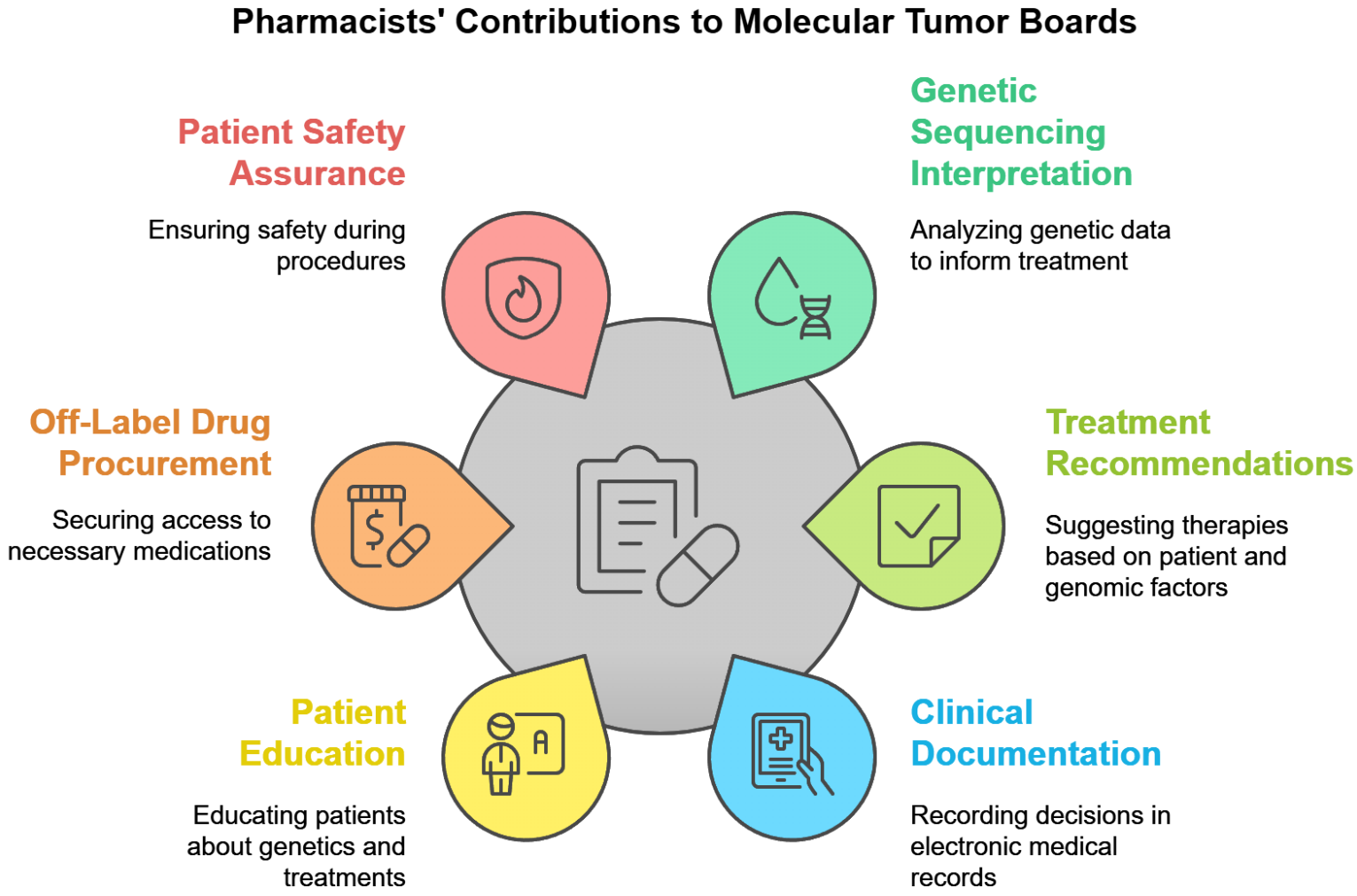
Table. Patients with actionable genetic alterations and recommendation of antineoplastic agent

No.	Cancer	Stage	Actionable genetic alterations	Treatment recommendation	Antineoplastic agent	ESCAT Level
1	Lung adenocarcinoma	IVB	*ERBB2 A775*	Clinical trial	BAY2927088	Tier 4
2	Lung adenocarcinoma	IVB	*MET, EGFR*	Off-label treatment	1st generation EGFR TKI plus Osimertinib	Tier 4
3	Lung adenocarcinoma	IIIA	*ALK* fusion	Standard treatment	ALK inhibitor	Tier 1
4	Lung adenocarcinoma	IIIC	*ALK* fusion, *ERBB2* amplification	Standard treatment	Brigatinib	Tier 1
5	Lung adenocarcinoma	IVA	*CD74-ROS 1* fusion	Standard treatment	Crizotinib	Tier 1
6	Lung adenocarcinoma	IVA	*EGFR T790M*	Standard treatment	Osimertinib	Tier 1
7	Lung adenocarcinoma	IIIC	*KRAS-G12C*, TMB high	Standard treatment	Sotorasib plus Pemrbolizumab	Tier 4
8	Lung squamous carcinoma	IVB	TMB-medium	Off-label treatment	Immunotherapy	Tier 4
9	Anaplastic astrocytoma	-	*IDH1* mutation, *MET* amplification	Off-label treatment	IDH 1 inhibitor	Tier 4
10	Endometrial cancer	IV	MSI-High, *PI3K* mutation	Standard treatment	Pembrolizumab	Tier 1
11	Oropharyngeal cancer	IVB	TMB-High	Standard treatment	Immunotherapy	Tier 1
12	Sarcomatoid Carcinoma	IV	PD-L1 (TPS:95; CPS:95)	Standard treatment	Nivolumab	Tier 1

ESCAT level: European Society for Medical Oncology Scale for Clinical Actionability of Molecular Targets (ESMO-ESCAT) tier level; Tier 1: Alteration-drug match is associated with improved outcome in clinical trials; Tier 4: Pre-clinical evidence of actionability.

Ann Oncol. 2018 Sep 1;29(9):1895-1902.

Pharmacist Role in MTB



Pharmacy (Basel). 2020 Mar 8;8(1):32.

Main Highlights and Takeaways

- Personalized Treatment with Molecular Profiling
  - Next-Generation Sequencing (NGS) identifies druggable mutations, guiding individualized cancer therapies
- Collaborative MTB Approach
  - Multidisciplinary team, including pharmacists, interprets genetic data to recommend patient-specific treatments, especially for complex cases
- Pharmacist’s Critical Role
  - Supports genomic interpretation, patient education, and off-label drug access, enhancing precision medicine's impact on patient care