Breast Pathology Course 2020 @21

Case 16

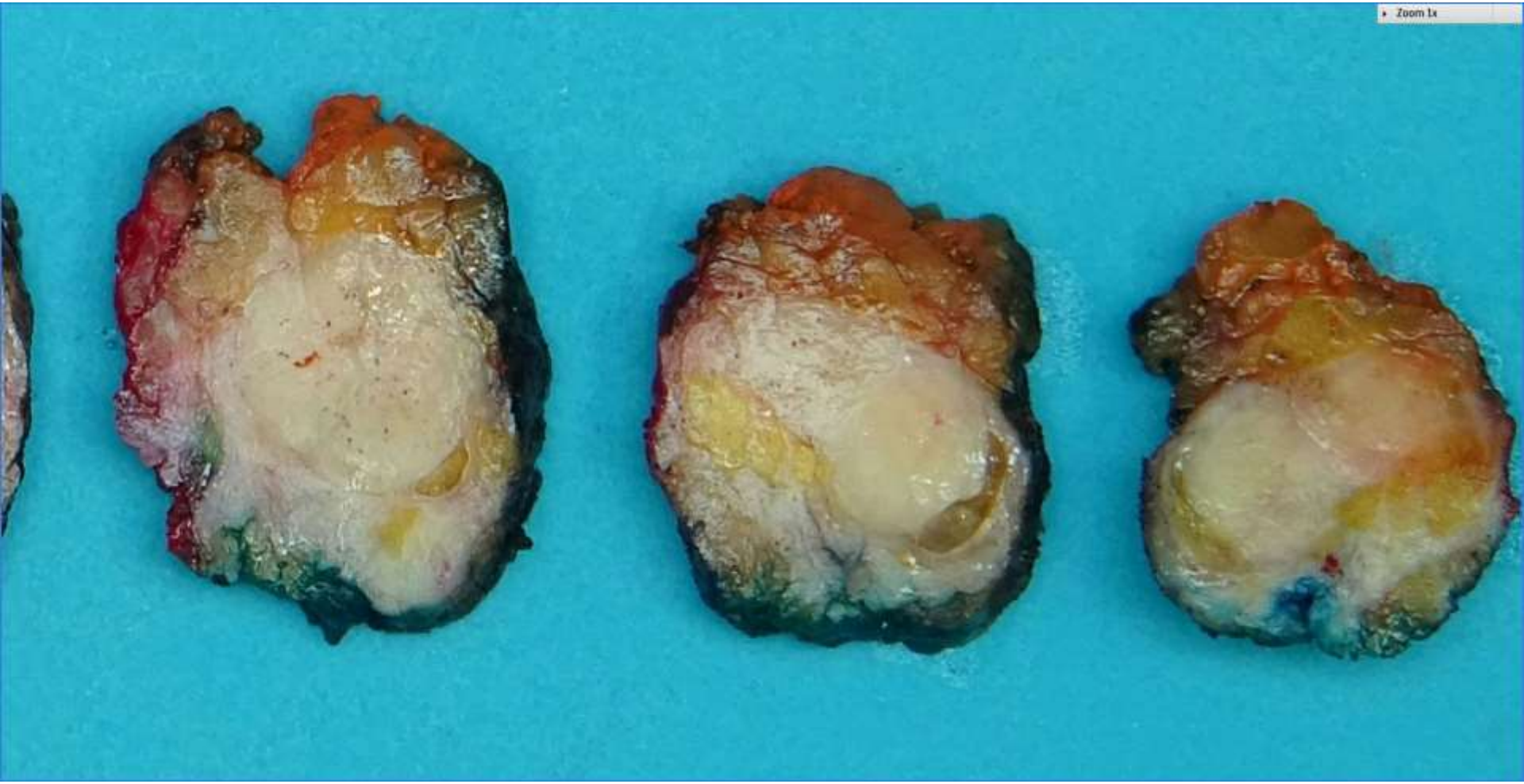
66 year old Chinese female.
Hookwire localization excision biopsy for a right breast 1 o'clock nodule and upper central calcifications.

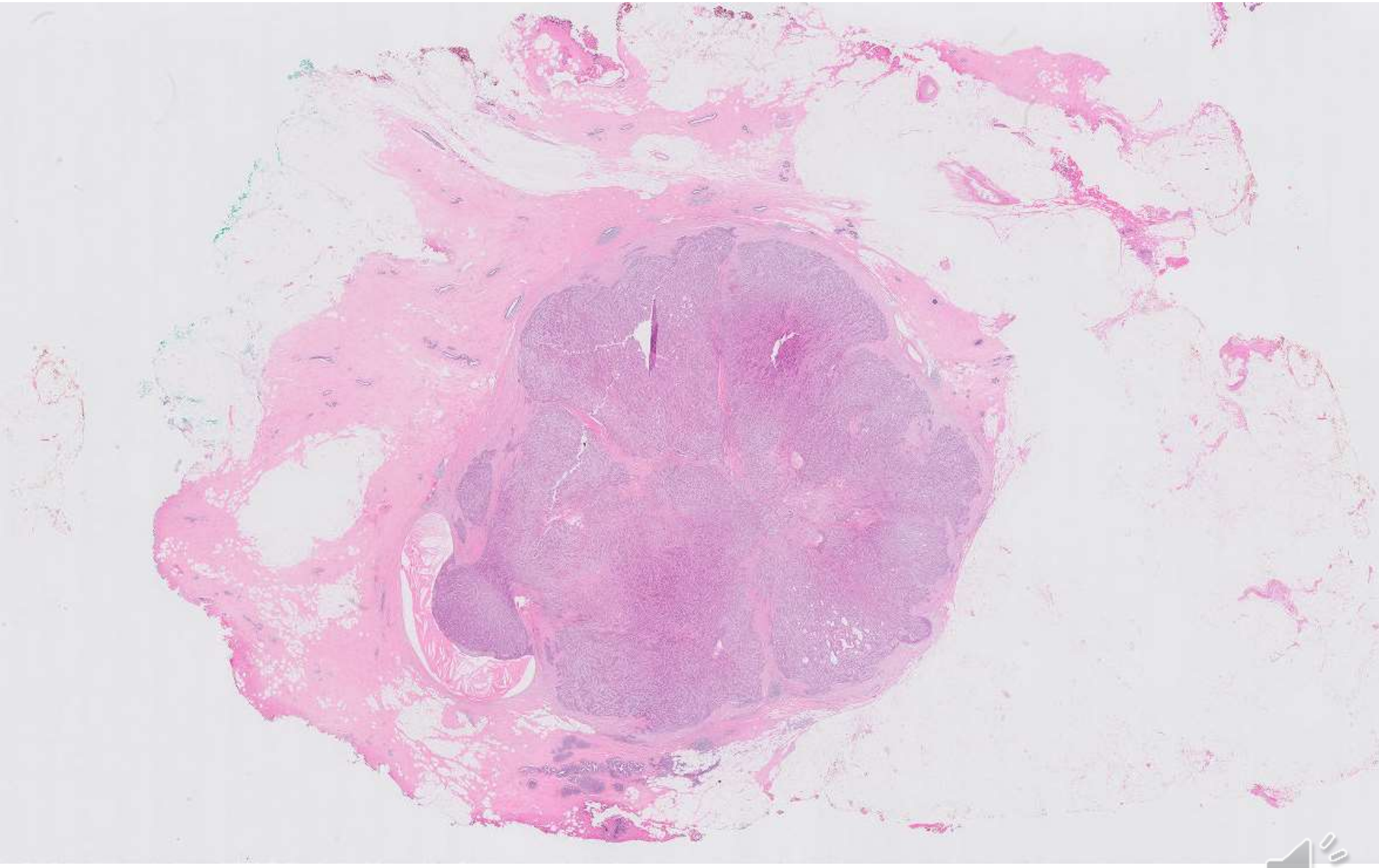
Presented by Timothy Tay

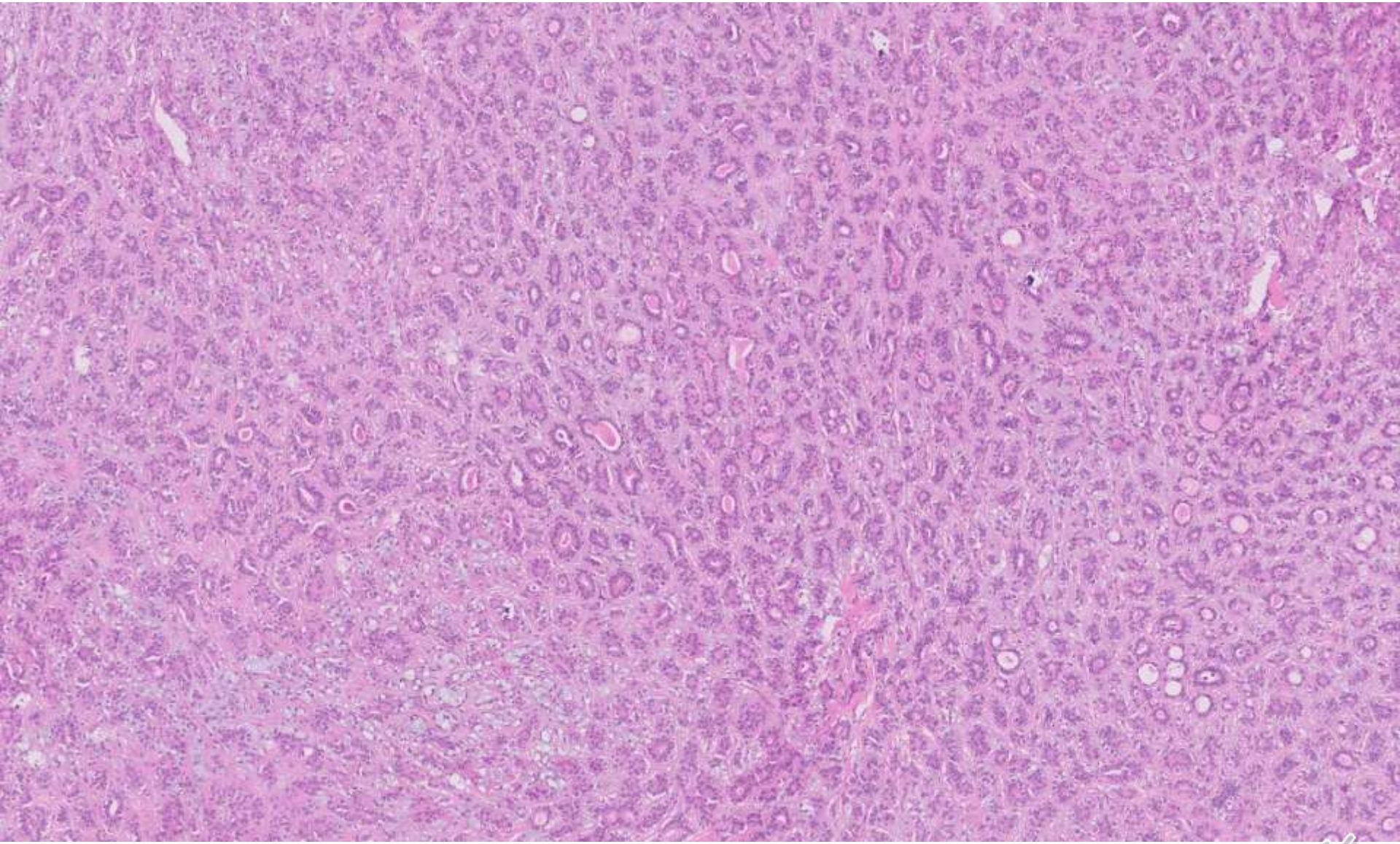
Division of Pathology
Singapore General Hospital

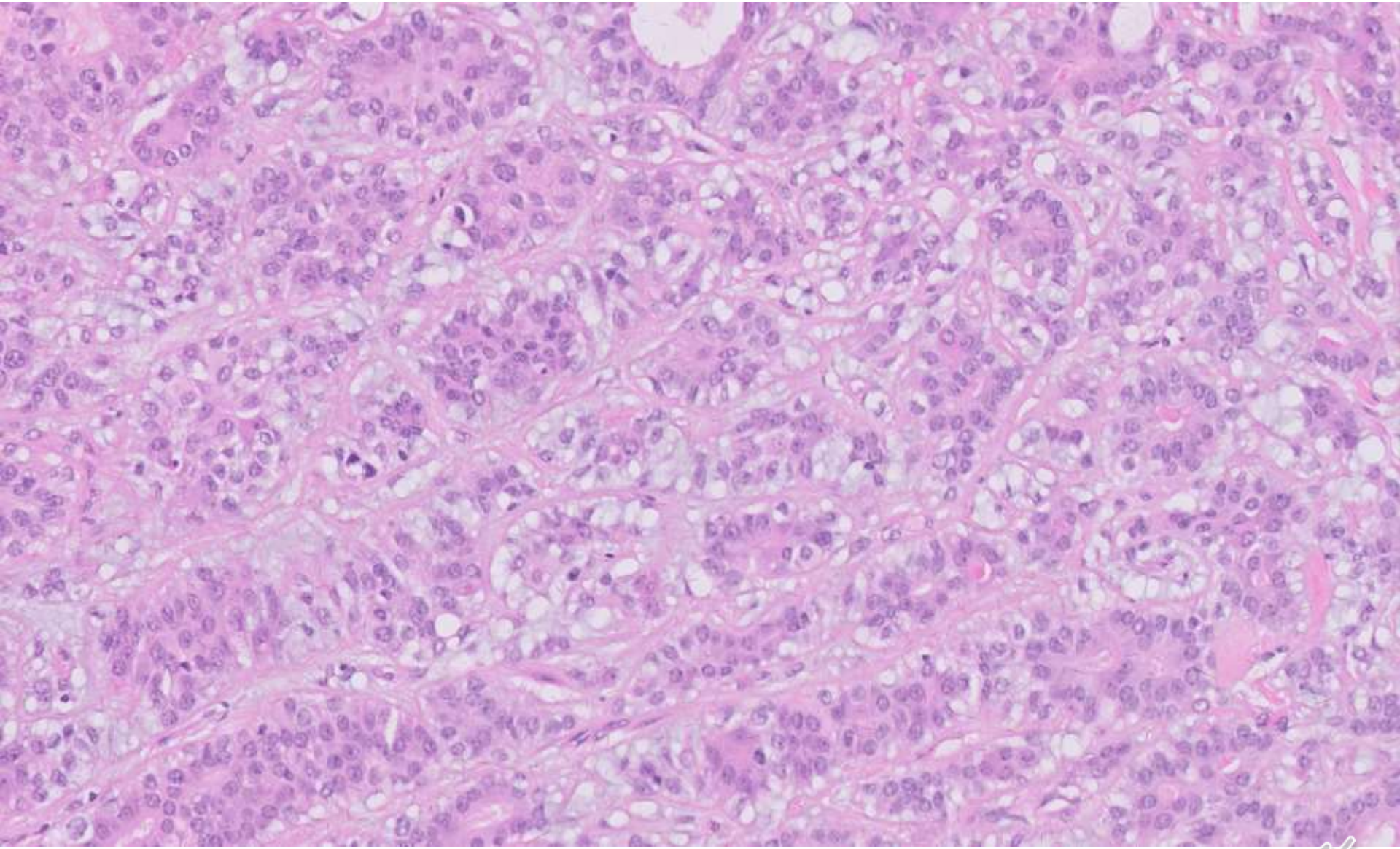
SingHealth DukeNUS
ACADEMIC MEDICAL CENTRE
PATHOLOGY

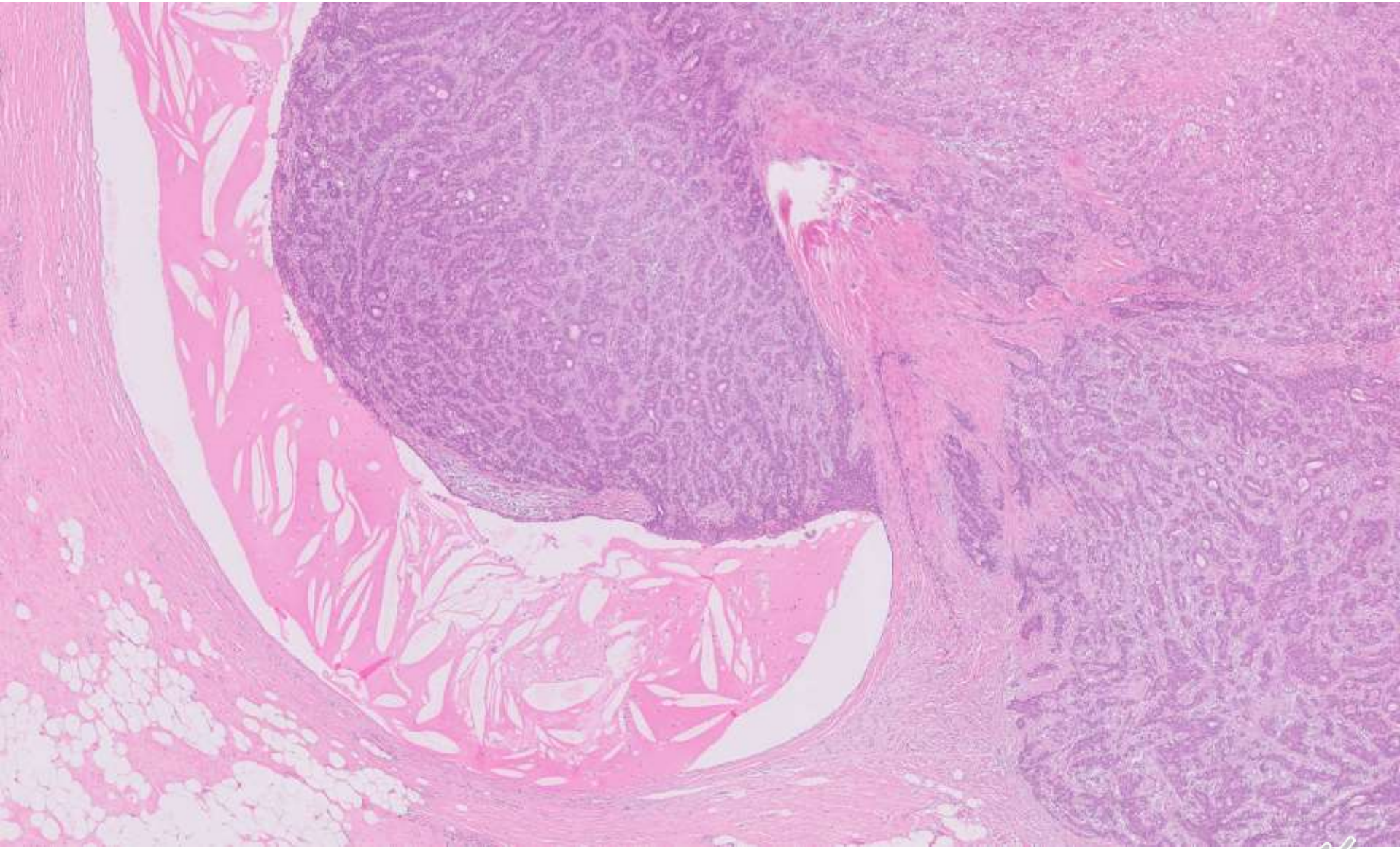
IAP
International Academy of Pathology
Singapore Division

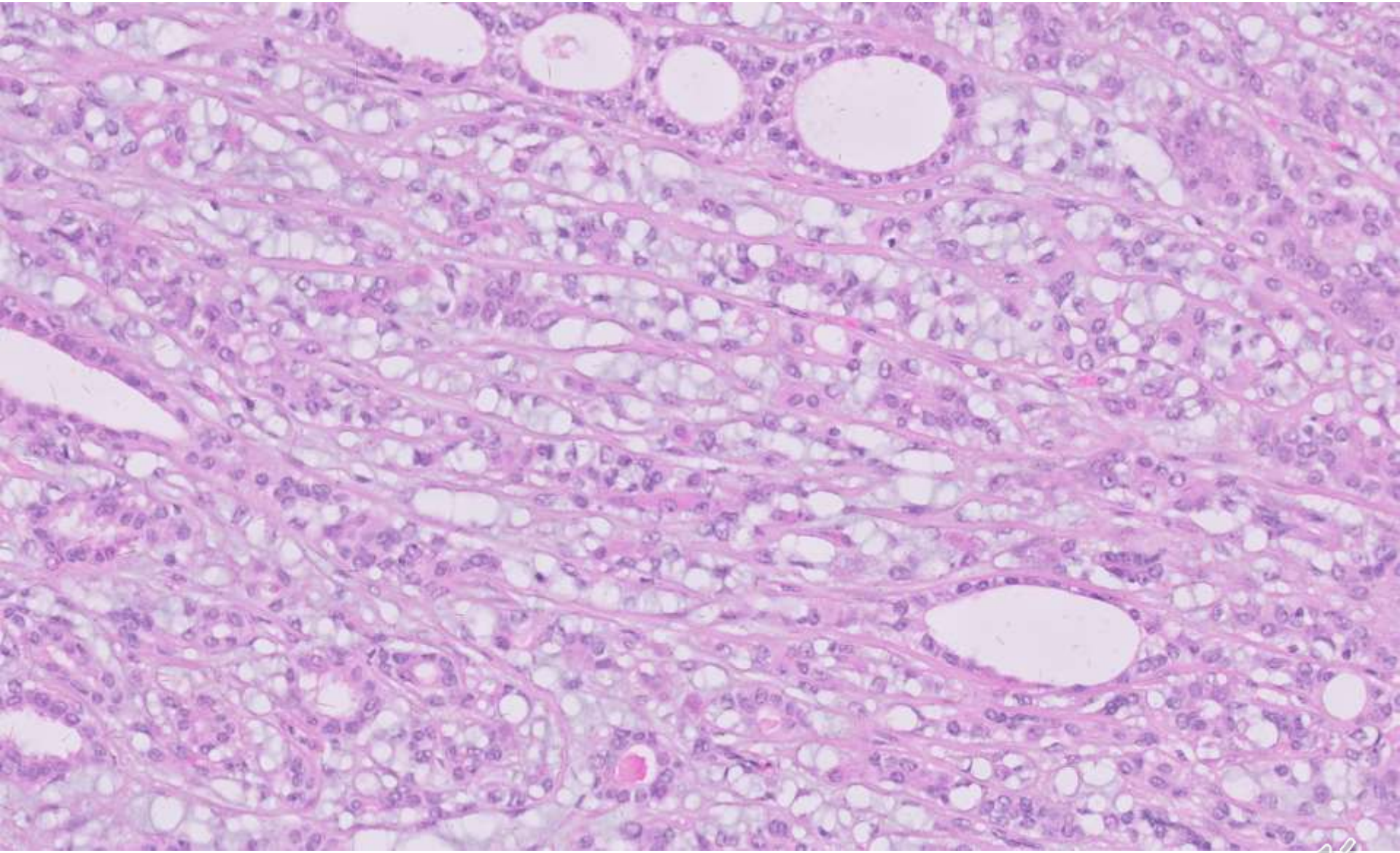

Zoom 1x











Diagnosis

- Adenomyoepithelioma

Molecular genetics

- In a study by Geyer et al. of 43 adenomyoepitheliomas of which 31 had whole exome sequencing or targeted next generation sequencing of 410 genes, *PIK3CA* hotspot mutations was found in 52% of adenomyoepitheliomas, *HRAS* mutations in 26% (p.Q61R or p.Q61K mutation), *AKT1* in 13% and *PIK3R1* mutation in 13% of tumours.
- AMEs had a lower mutation burden/fewer somatic mutations compared to invasive breast cancers.

Molecular genetics

- ER-positive and ER-negative AMEs have different mutational profiles.
- *AKT1* (p.E17K) mutation was seen only in ER-positive AMEs.
- *HRAS* and *PIK3R1* mutations were seen only in ER-negative AMEs.
- *PIK3CA* mutation was seen in both.
- HRAS mutations in ER-negative AME was significantly associated with necrosis and increased mitotic activity.
- ER-negative AMEs also had higher number of somatic mutations compared to ER-positive AMEs, although the difference did not reach statistical significance.

nature COMMUNICATIONS

ARTICLE

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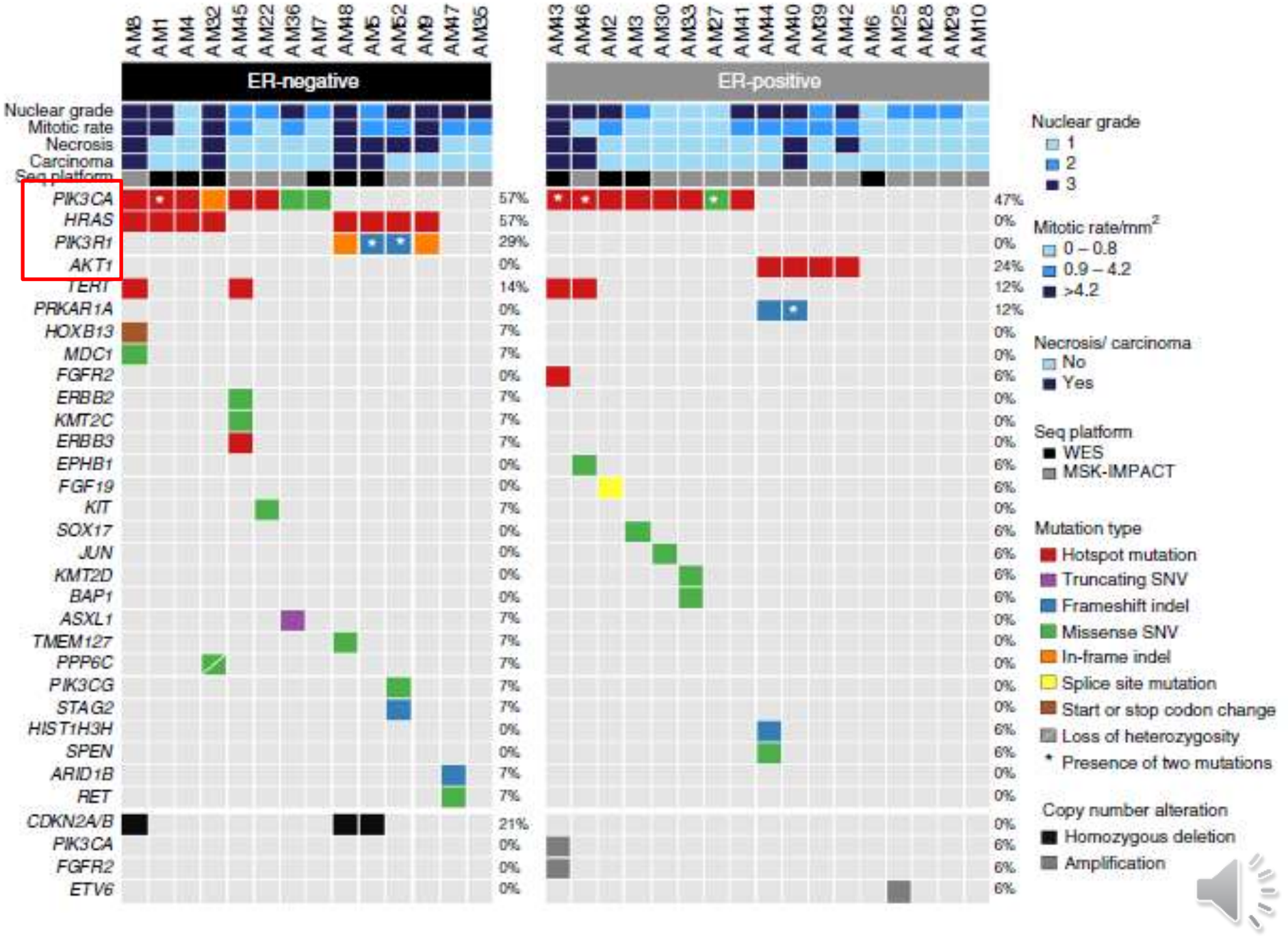
Recurrent hotspot mutations in *HRAS* Q61 and PI3K-AKT pathway genes as drivers of breast adenomyoepitheliomas

Felipe C. Geyer[1,2,3], Anqi Li[1,4], Anastasios D. Papanastasiou[1,5], Alison Smith[6], Pier Selenica[1], Kathleen A. Burke[1], Marcia Edelweiss[1], Huei-Chi Wen[1], Salvatore Piscuoglio[1,7], Anne M. Schultheis[1], Luciano G. Martelotto[1], Fresia Pareja[1], Rahul Kumar[1], Alissa Brandes[1], Dan Fan[1,8], Thais Basili[1], Arnaud Da Cruz Paula[1], John R. Lozada[1], Pedro Blecua[9], Simone Muenst[7], Achim A. Jungbluth[1], Maria P. Foschini[10], Hannah Y. Wen[1], Edi Brogi[1], Juan Palazzo[11], Brian P. Rubin[12], Charlotte K.Y. Ng[1,7,13], Larry Norton[14], Zsuzsanna Varga[15], Ian O. Ellis[16], Emad A. Rakha[16], Sarat Chandarlapaty[6], Britta Weigelt[1] & Jorge S. Reis-Filho[1,6]


AM8 AM1 AM4 AM32 AM45 AM22 AM36 AM7 AM48 AM5 AM52 AM9 AM47 AM35
ER-negative
AM43 AM46 AM2 AM3 AM30 AM33 AM27 AM41 AM44 AM40 AM39 AM42 AM6 AM25 AM28 AM29 AM10
ER-positive
Nuclear grade
Mitotic rate
Necrosis
Carcinoma
Seq platform
PIK3CA 57% 47%
HRAS 57% 0%
PIK3R1 29% 0%
AKT1 0% 24%
TERT 14% 12%
PRKAR1A 0% 12%
HOXB13 7% 0%
MDC1 7% 0%
FGFR2 0% 6%
ERBB2 7% 0%
KMT2C 7% 0%
ERBB3 7% 0%
EPHB1 0% 6%
FGF19 0% 6%
KIT 7% 0%
SOX17 0% 6%
JUN 0% 6%
KMT2D 0% 6%
BAP1 0% 6%
ASXL1 7% 0%
TMEM127 7% 0%
PPP6C 7% 0%
PIK3CG 7% 0%
STAG2 7% 0%
HIST1H3H 0% 6%
SPEN 0% 6%
ARID1B 7% 0%
RET 7% 0%
CDKN2A/B 21% 0%
PIK3CA 0% 6%
FGFR2 0% 6%
ETV6 0% 6%
Nuclear grade
1
2
3
Mitotic rate/mm2
0 – 0.8
0.9 – 4.2
>4.2
Necrosis/ carcinoma
No
Yes
Seq platform
WES
MSK-IMPACT
Mutation type
Hotspot mutation
Truncating SNV
Frameshift indel
Missense SNV
In-frame indel
Splice site mutation
Start or stop codon change
Loss of heterozygosity
* Presence of two mutations
Copy number alteration
Homozygous deletion
Amplification

Molecular genetics

- Interestingly, papillomas without atypia which overlaps morphologically with ER-positive AME with papillary architecture have also been found to harbour *PIK3CA* and *AKT1* mutation in a separate study.
- *HRAS* p.Q61 mutations which occur in ER-negative tumours have also been reported in morphologically similar epithelial-myoepithelial carcinomas of the salivary gland.
- In a subsequent study by the same group, an AME that was wildtype for *PIK3CA*, *AKT1* and *HRAS* mutations was found to harbour a *HMGA2-WIF1* fusion, previously described in pleomorphic adenomas of the salivary gland.

npj | Breast Cancer

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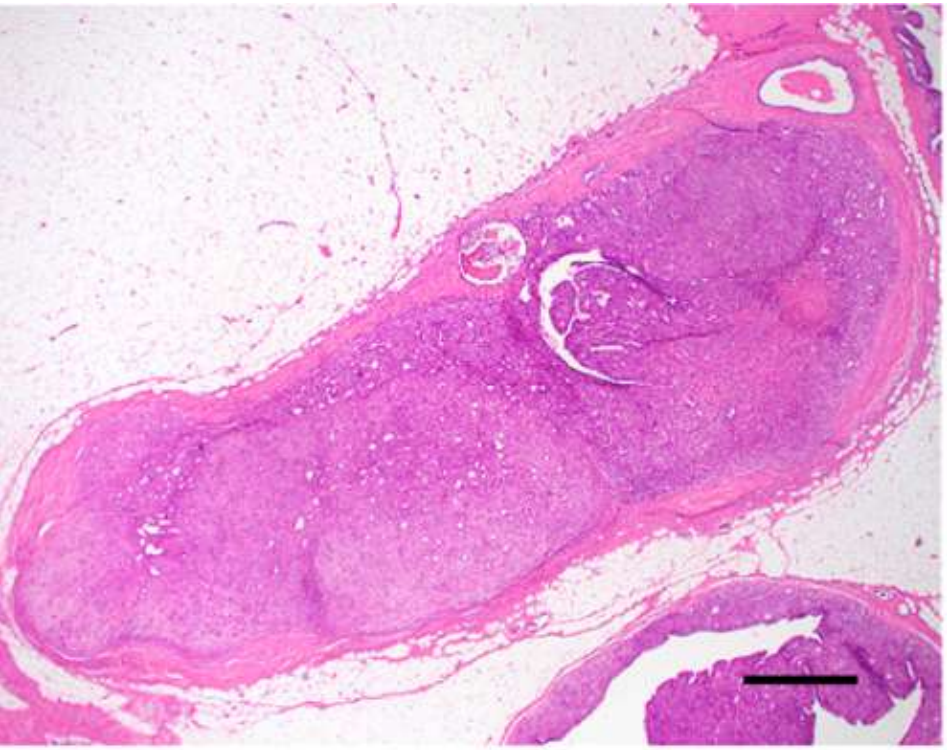
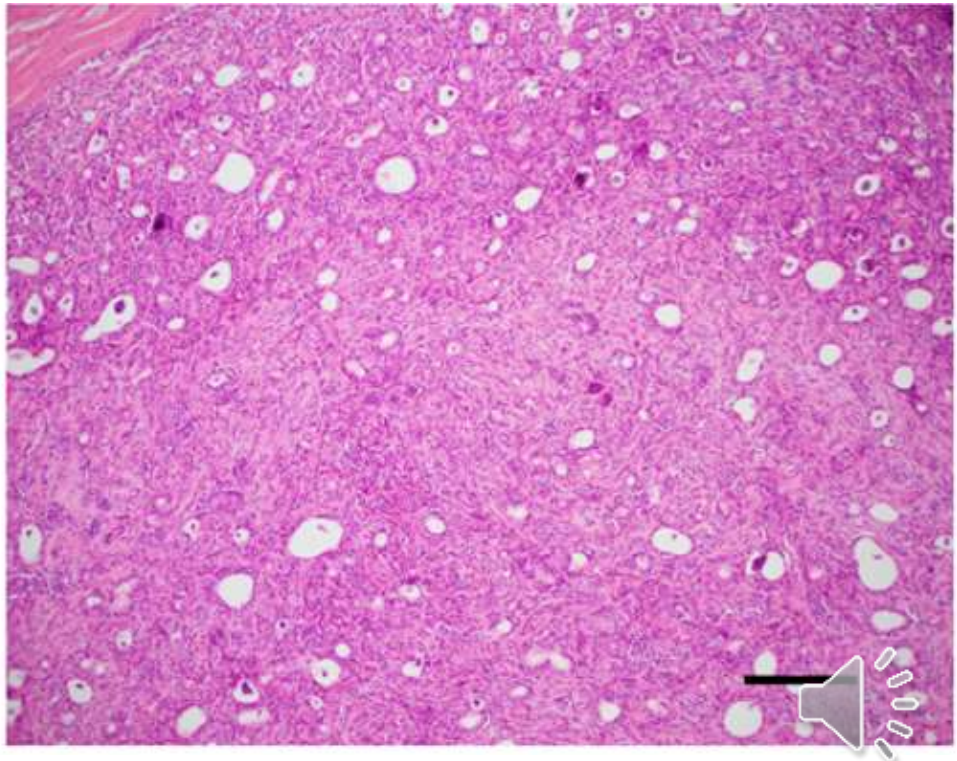
ARTICLE OPEN

Assessment of *HMGA2* and *PLAG1* rearrangements in breast adenomyoepitheliomas

Fresia Pareja[1], Felipe C. Geyer[1], David N. Brown[1], Ana P. Martins Sebastião[1], Rodrigo Gularte-Mérida[1], Anqi Li[1], Marcia Edelweiss[1], Arnaud Da Cruz Paula[1], Pier Selenica[1], Hannah Y. Wen[1], Achim A. Jungbluth[1], Zsuzsanna Varga[2], Juan Palazzo[3], Brian P. Rubin[4], Ian O. Ellis[5], Edi Brogi[1], Emad A. Rakha[5], Britta Weigelt[1] and Jorge S. Reis-Filho[1]





Prognosis

- Majority of AMEs are benign and excision with clear margins are curative.
- Tumours with extensive intraductal growth or satellite nodules may recur
- AMEs with benign histology have also been reported to metastasize to distant sites in very rare instances.

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Thank You

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