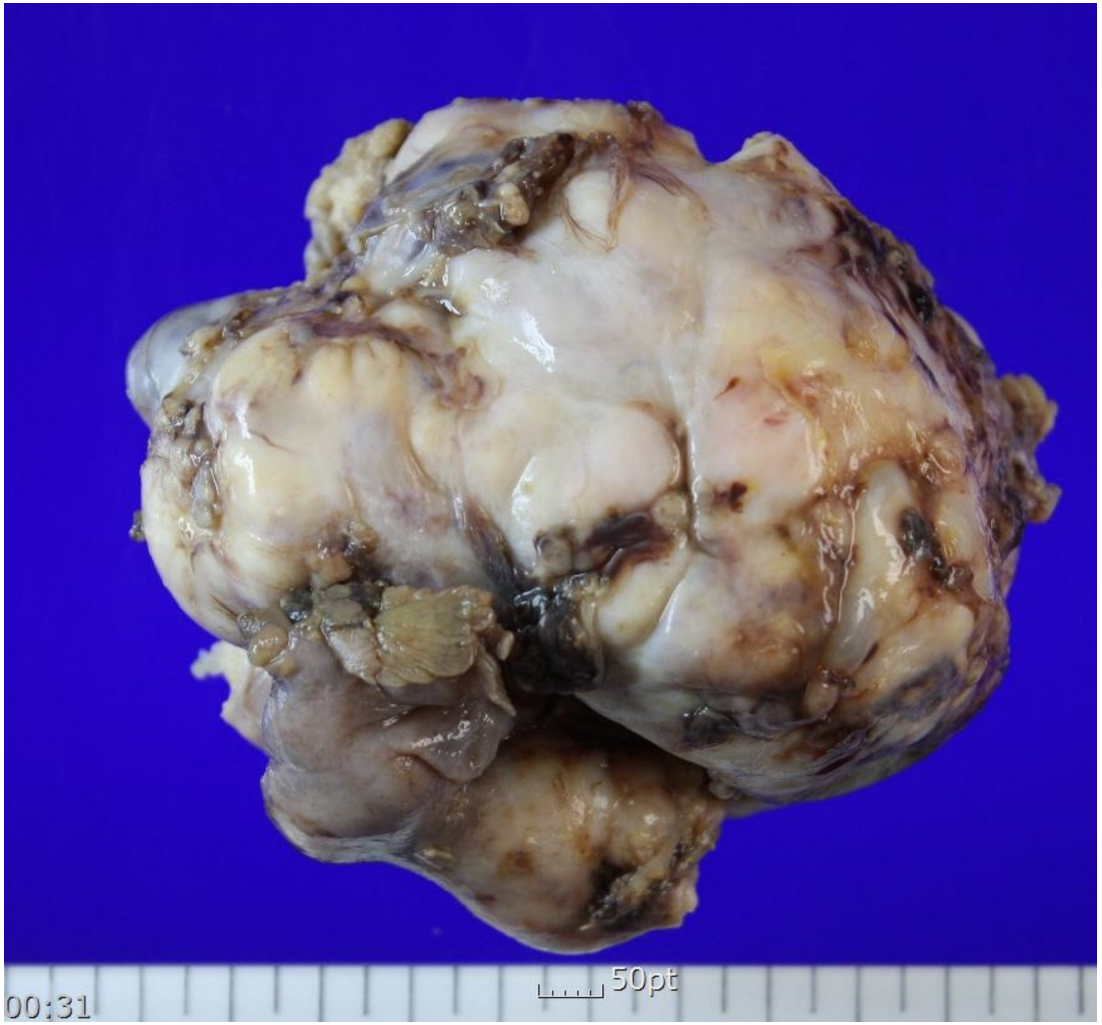
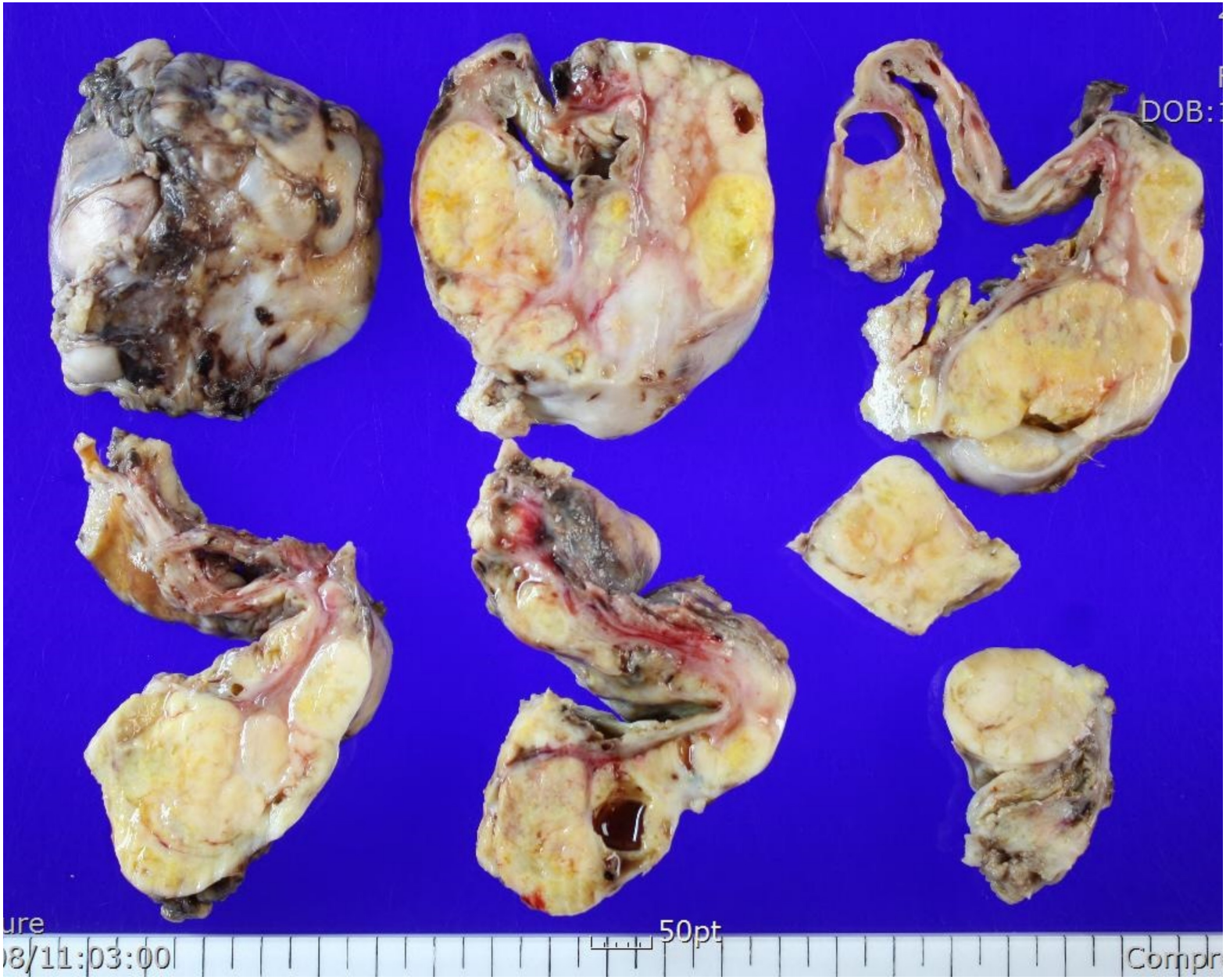
Pathology

Case study

Jun Kang

Case1




DOB:
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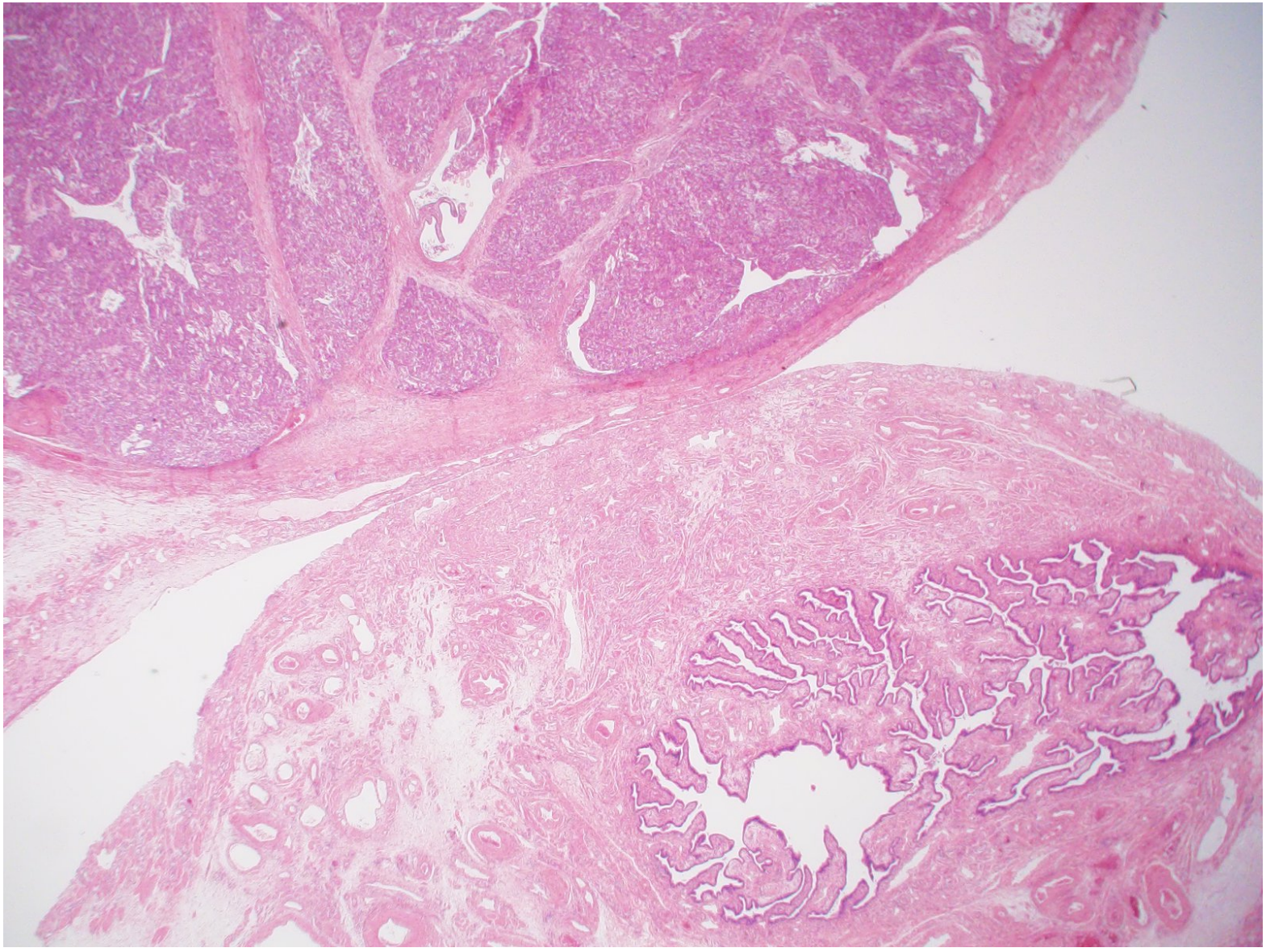
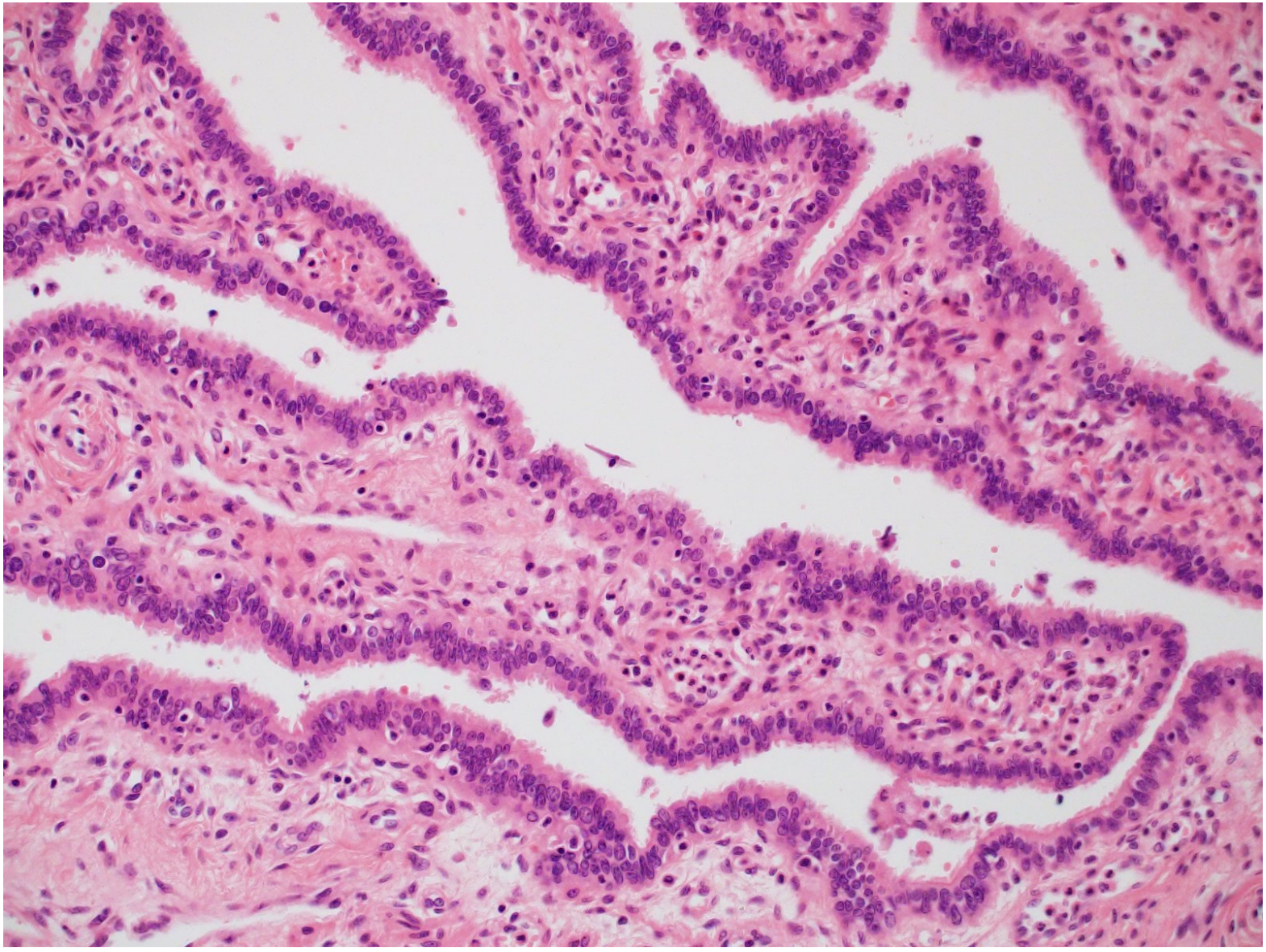
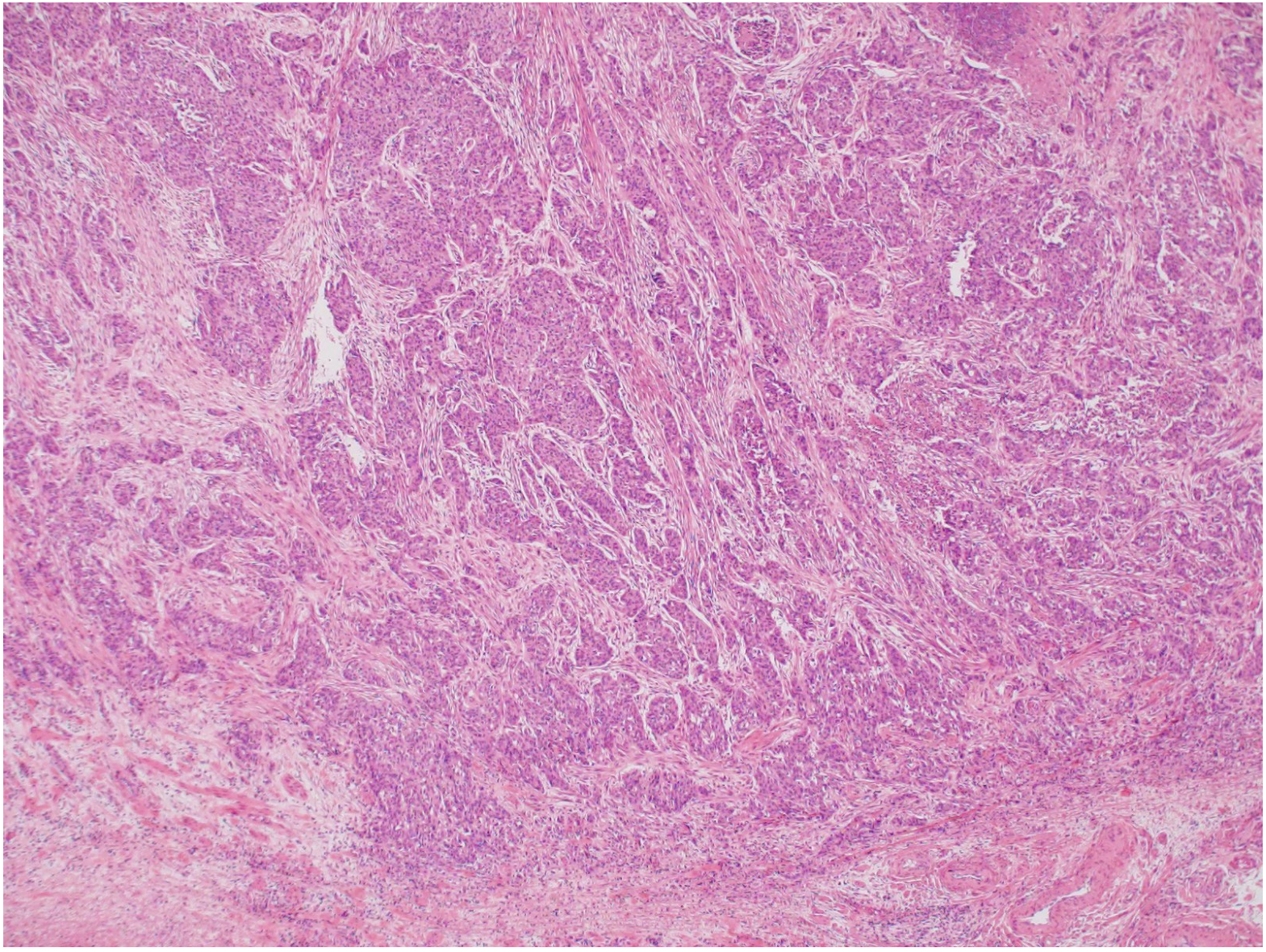
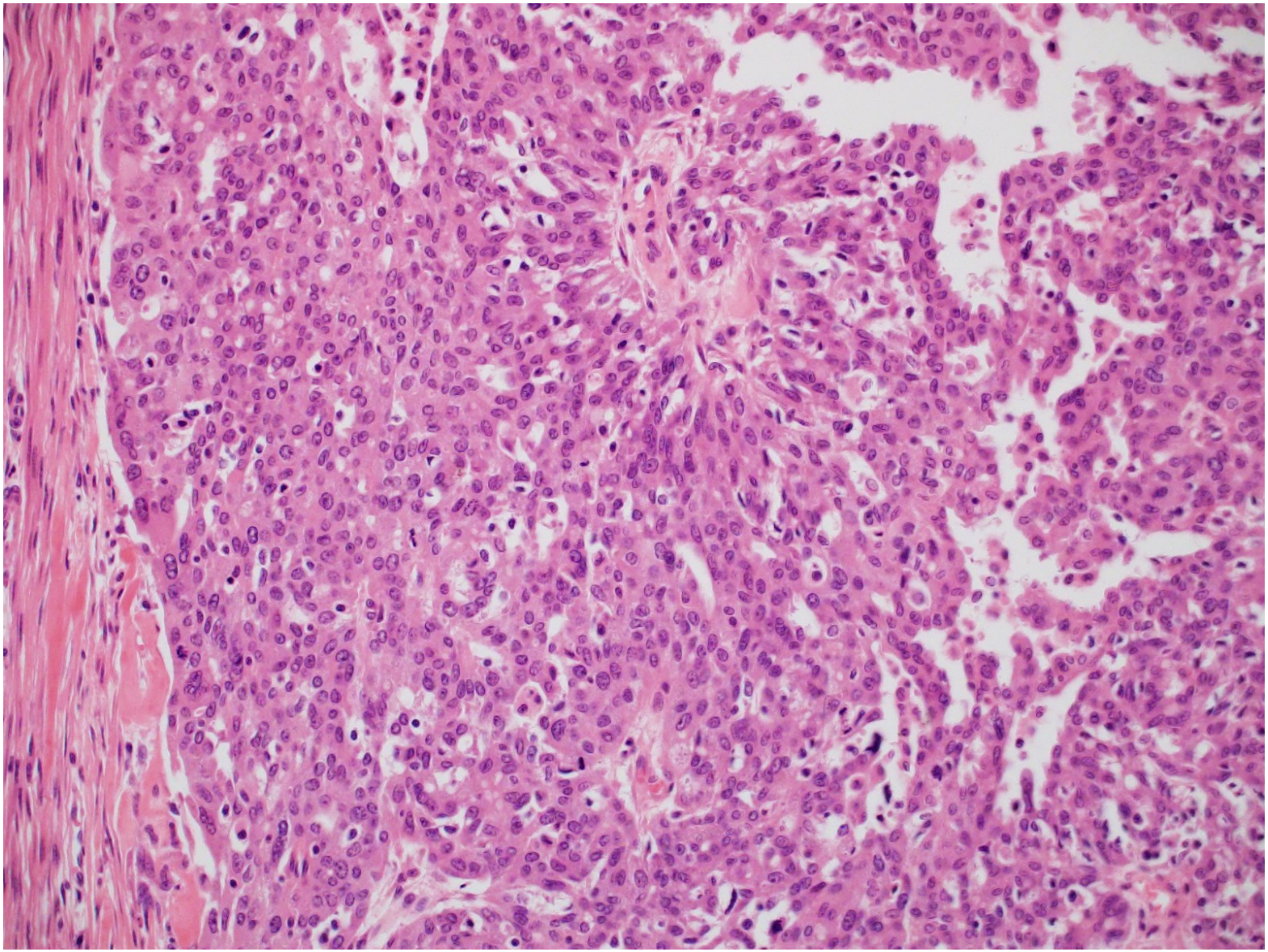
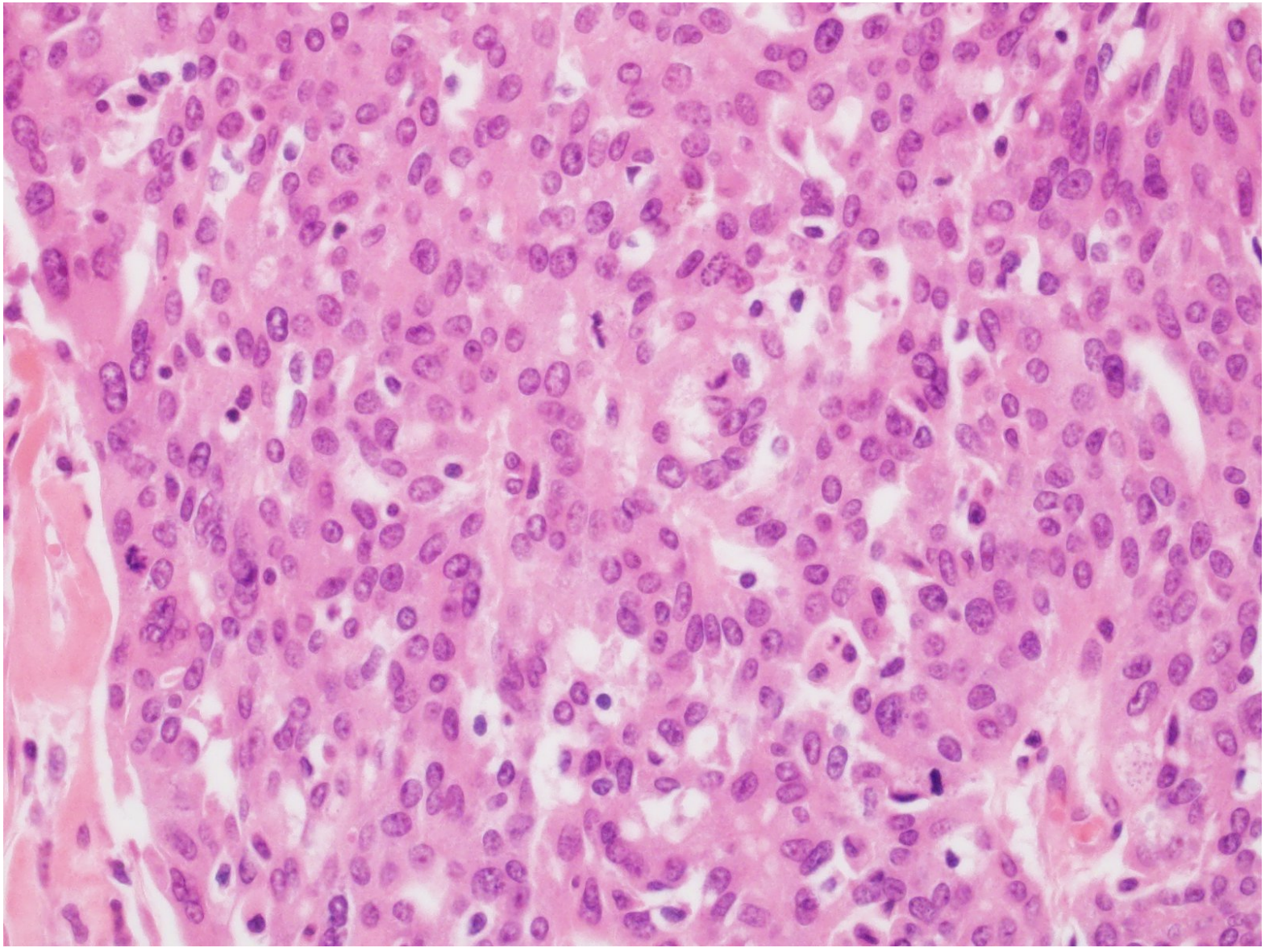
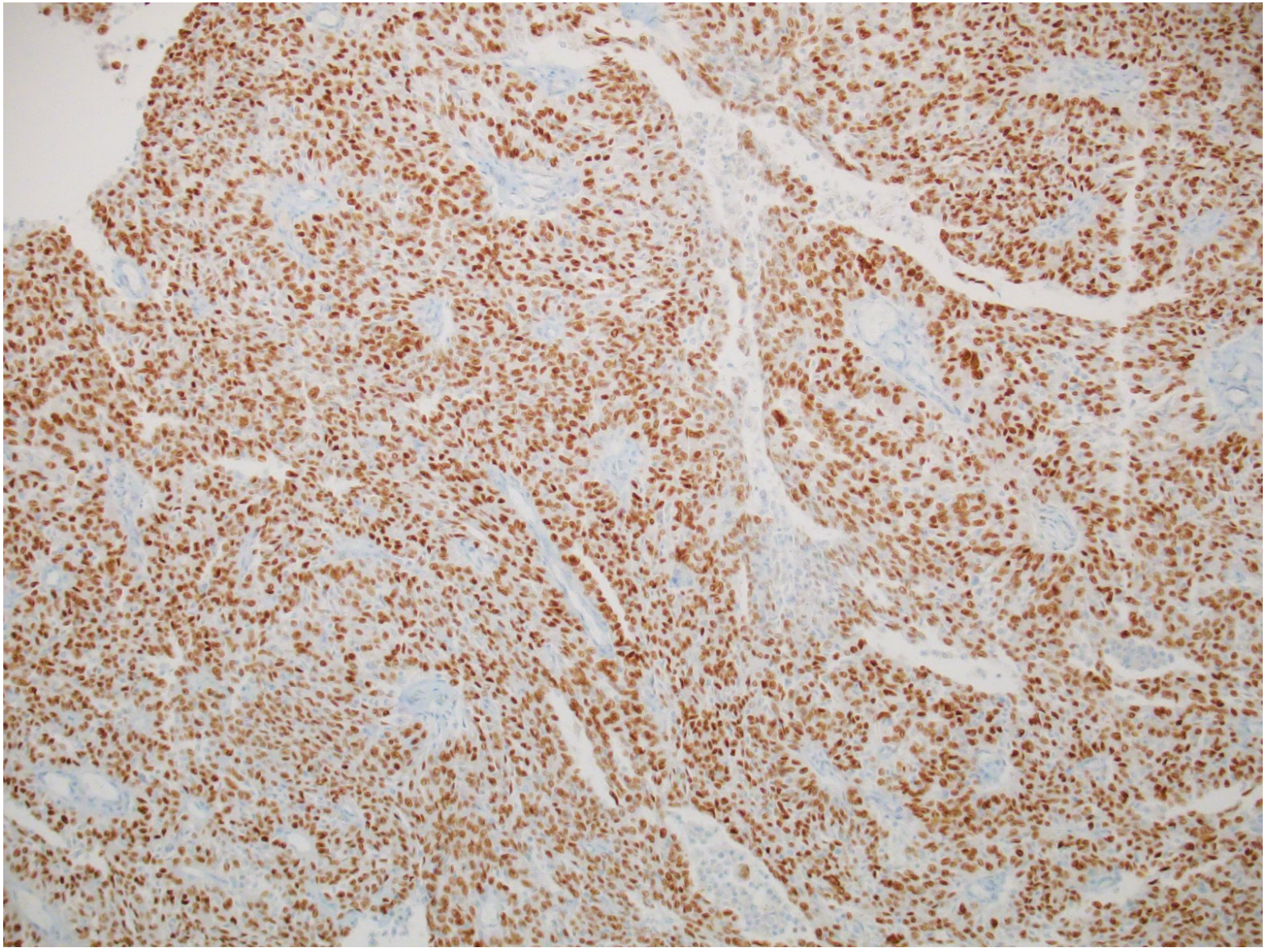






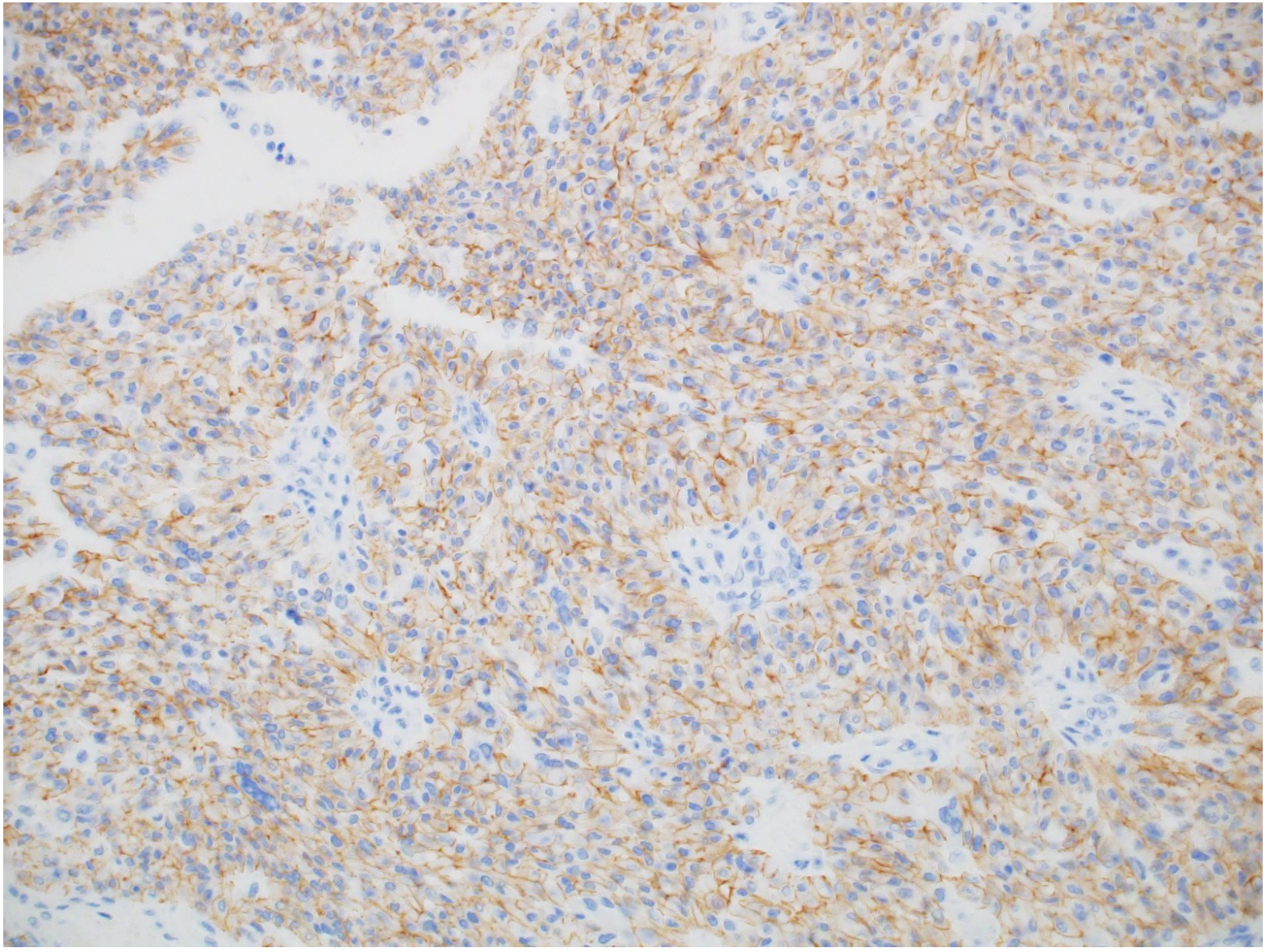






p53

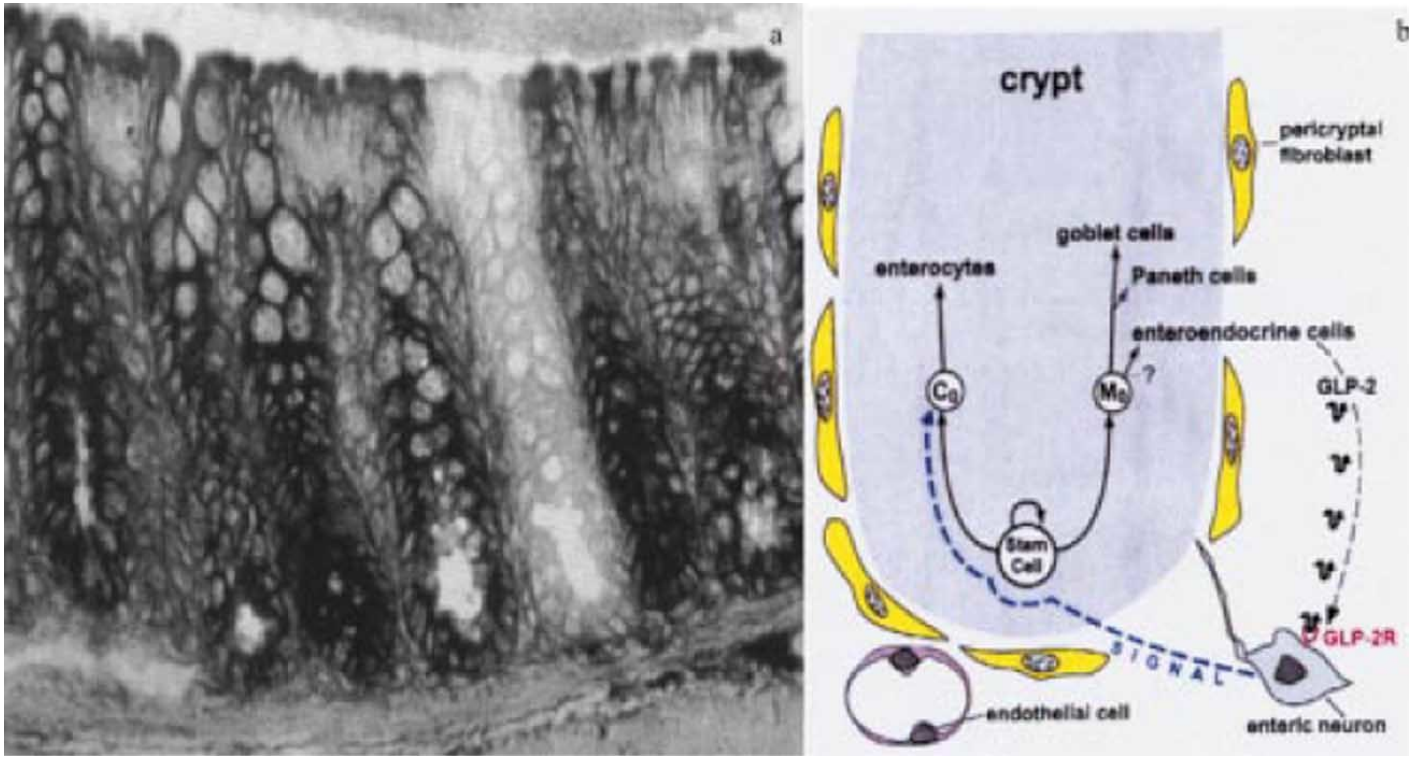
- DNA damage and repair
  - Regulation or progression through the cell cycle
  - Apoptosis
  - Genomic stability
- Mutation
  - Null-type
  - Gain-of-function
  - 95% of high-grade serous carcinoma



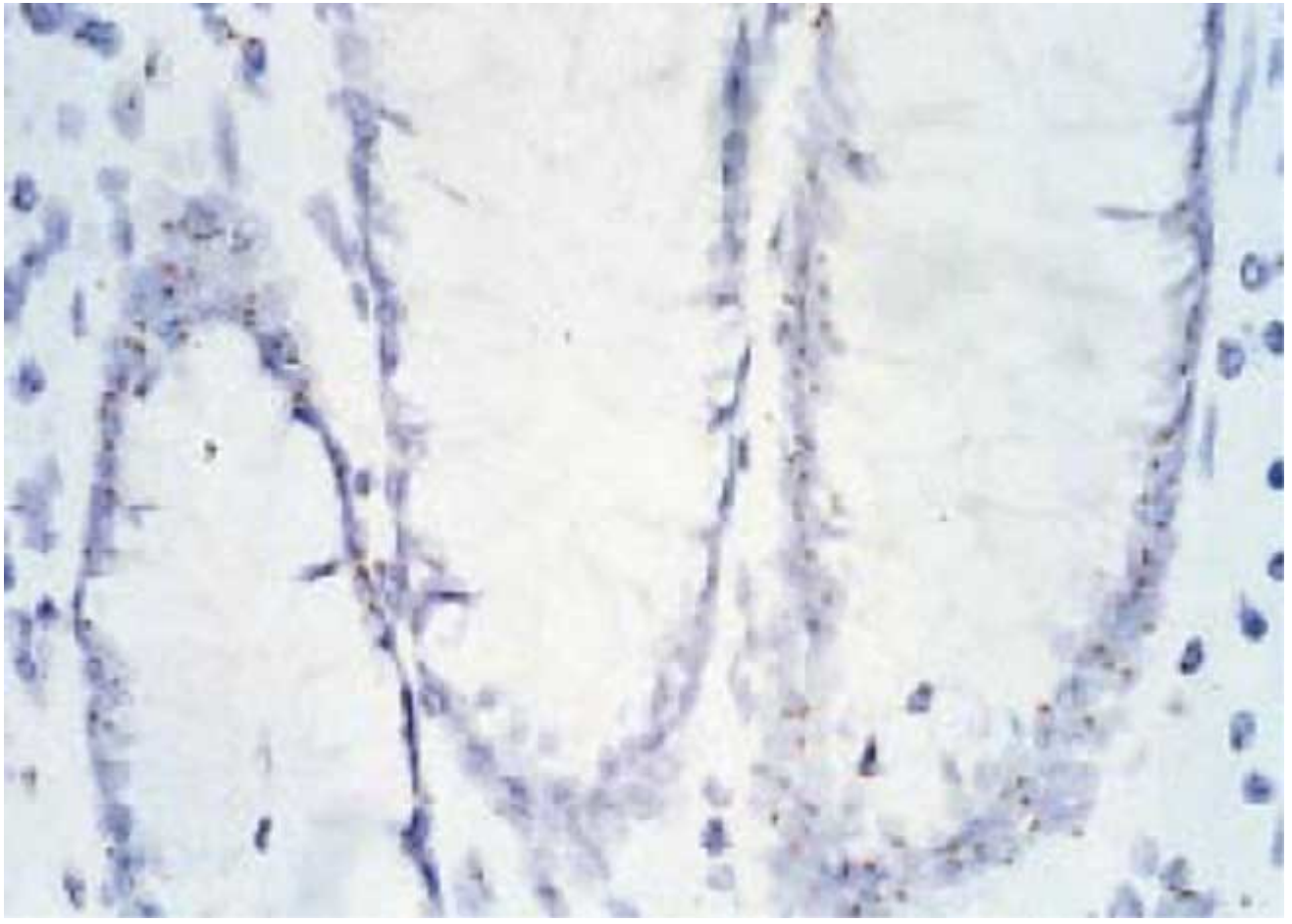
E-cadherin

- Key component of the **adherens junctions** that are integral in **cell-cell adhesion**
- As a marker of epithelium
- Loss of E-cadherin in some cancers
  - Lobular carinoma of breast
  - Poorly cohesive carcinoma of stomach

The stem cell niche hypothesis

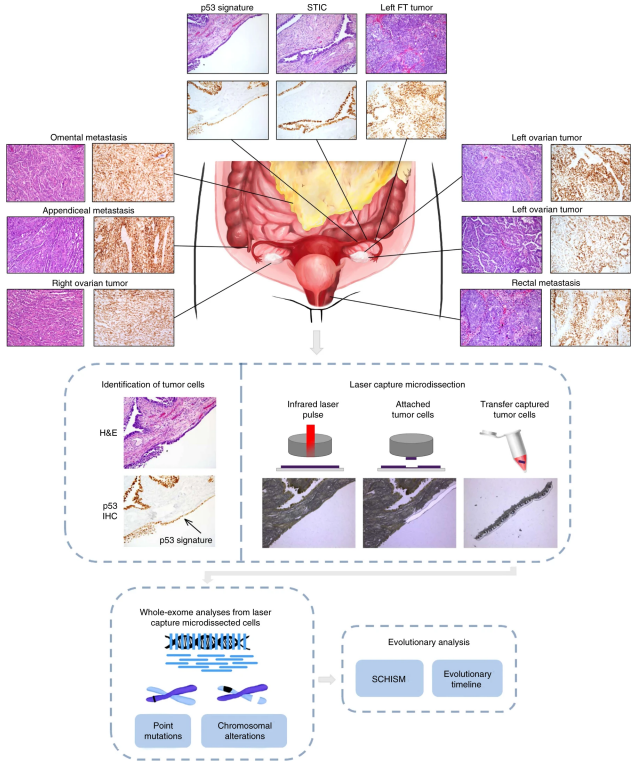


Monoclonal origin of colonic crypts in an XO/XY patient

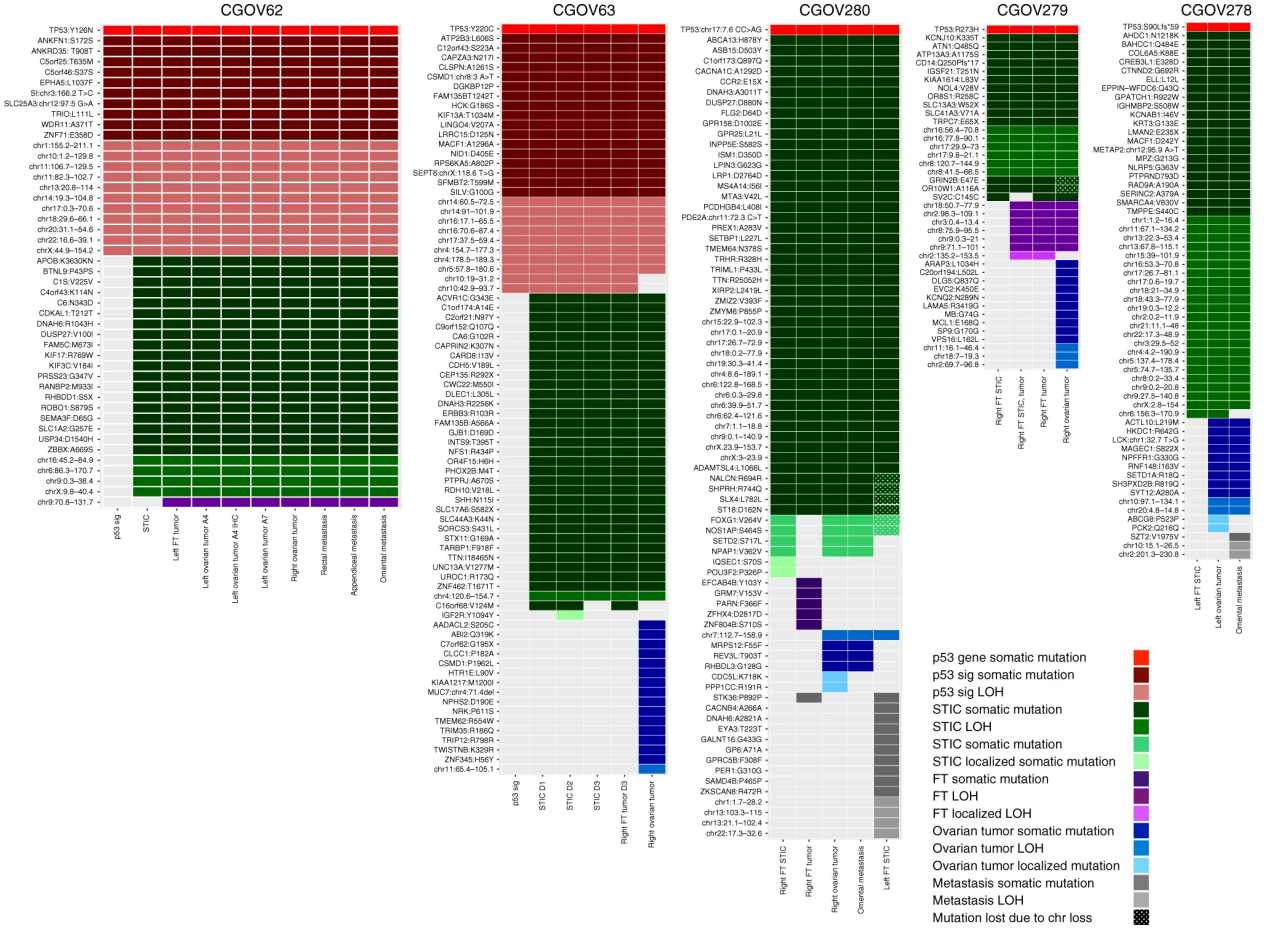


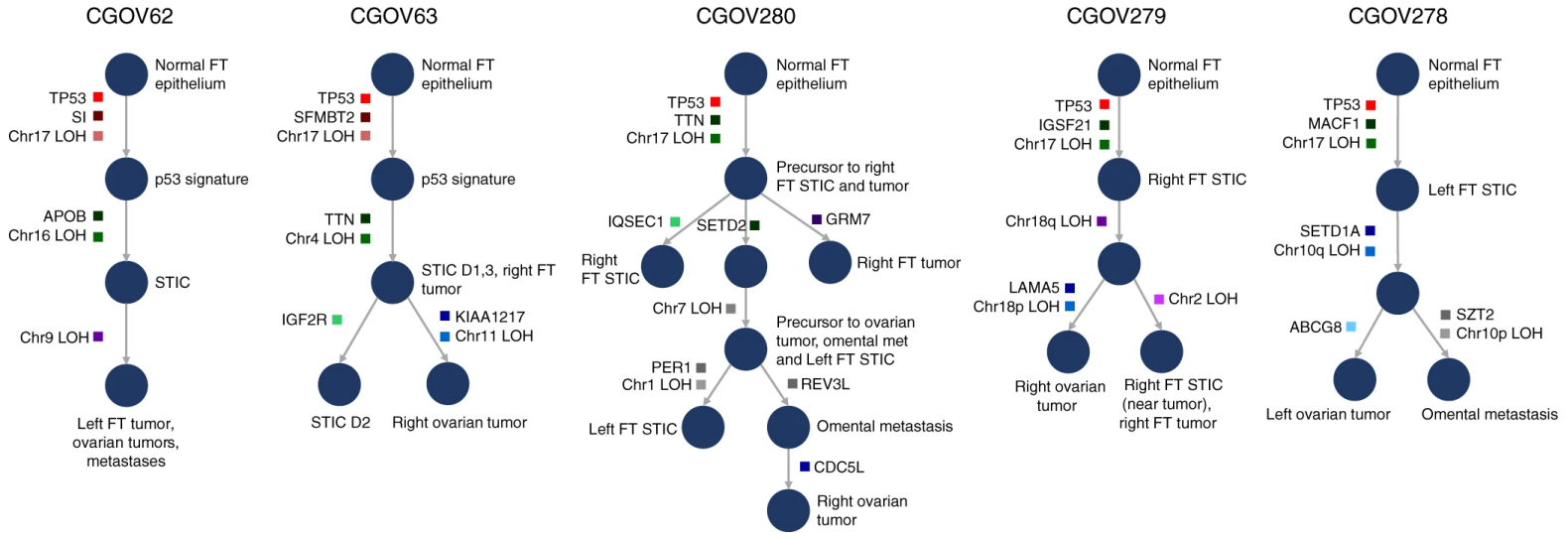
Robbins definition

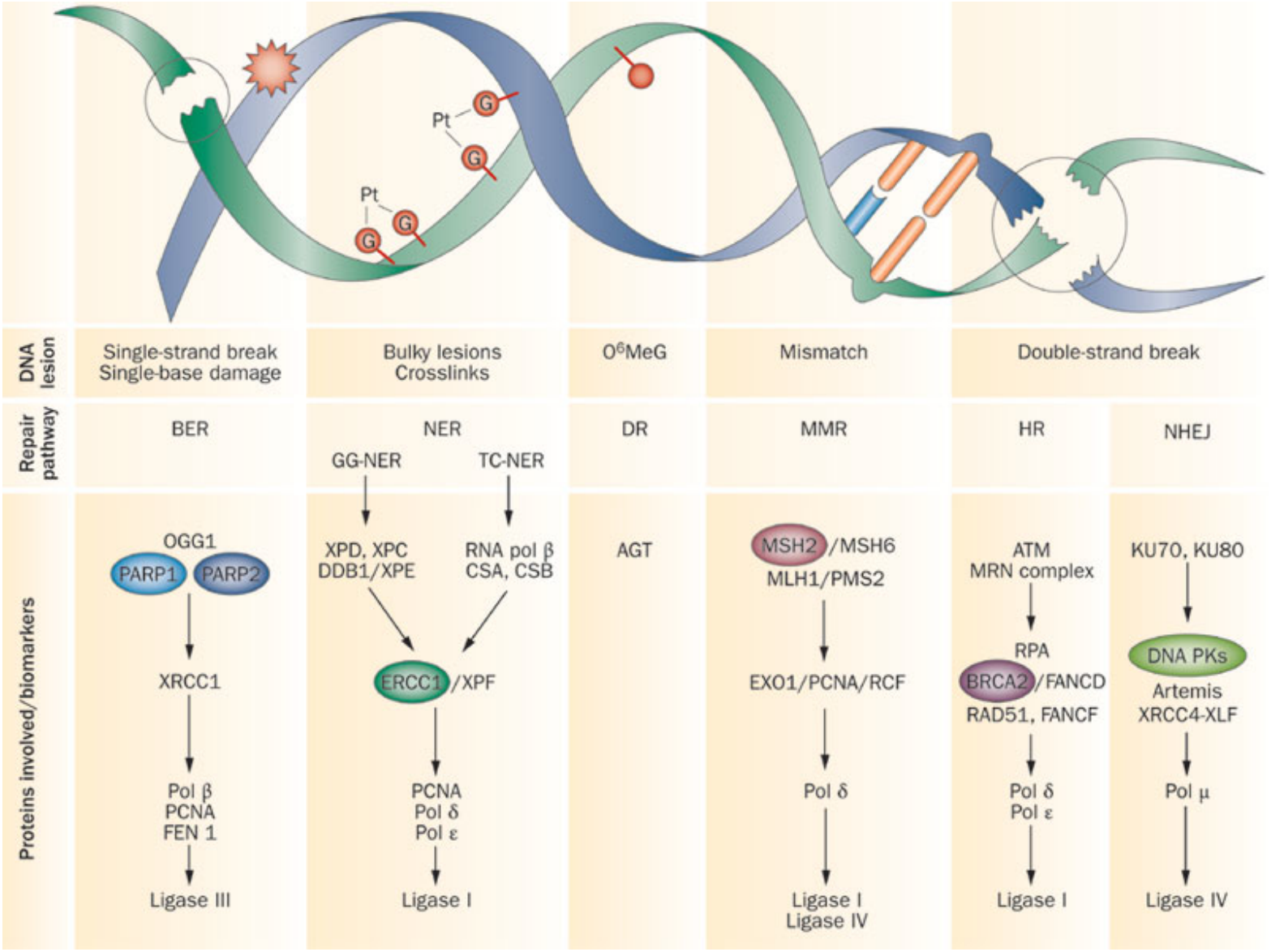
> A neoplasm is defined as a genetic disorder of cell growth that is triggered by acquired or less commonly inherited mutations affecting a single cell and its clonal progeny.



Nature Communications volume 8, Article number: 1093 (2017)


CGOV62
CGOV63
CGOV280
CGOV279
CGOV278
p53 gene somatic mutation
p53 sig somatic mutation
p53 sig LOH
STIC somatic mutation
STIC LOH
STIC somatic mutation
STIC localized somatic mutation
FT somatic mutation
FT LOH
FT localized LOH
Ovarian tumor somatic mutation
Ovarian tumor LOH
Ovarian tumor localized mutation
Metastasis somatic mutation
Metastasis LOH
Mutation lost due to chr loss


CGOV62
Normal FT epithelium
TP53
SI
Chr17 LOH
p53 signature
APOB
Chr16 LOH
STIC
Chr9 LOH
Left FT tumor, ovarian tumors, metastases
CGOV63
Normal FT epithelium
TP53
SFMBT2
Chr17 LOH
p53 signature
TTN
Chr4 LOH
STIC D1,3, right FT tumor
IGF2R
KIAA1217
Chr11 LOH
STIC D2
Right ovarian tumor
CGOV280
Normal FT epithelium
TP53
TTN
Chr17 LOH
Precursor to right FT STIC and tumor
IQSEC1
SETD2
GRM7
Right FT STIC
Right FT tumor
Chr7 LOH
Precursor to ovarian tumor, omental met and Left FT STIC
PER1
Chr1 LOH
REV3L
Left FT STIC
Omental metastasis
CDC5L
Right ovarian tumor
CGOV279
Normal FT epithelium
TP53
IGSF21
Chr17 LOH
Right FT STIC
Chr18q LOH
LAMA5
Chr18p LOH
Chr2 LOH
Right ovarian tumor
Right FT STIC (near tumor), right FT tumor
CGOV278
Normal FT epithelium
TP53
MACF1
Chr17 LOH
Left FT STIC
SETD1A
Chr10q LOH
ABCG8
SZT2
Chr10p LOH
Left ovarian tumor
Omental metastasis


Pt
G
G
Pt
G
G
DNA lesion
Single-strand break
Single-base damage
Bulky lesions
Crosslinks
O6MeG
Mismatch
Double-strand break
Repair pathway
BER
NER
GG-NER
TC-NER
DR
MMR
HR
NHEJ
Proteins involved/biomarkers
OGG1
PARP1
PARP2
XRCC1
Pol β
PCNA
FEN 1
Ligase III
XPD, XPC
DDB1/XPE
RNA pol β
CSA, CSB
ERCC1/XPF
PCNA
Pol δ
Pol ε
Ligase I
AGT
MSH2/MSH6
MLH1/PMS2
EXO1/PCNA/RCF
Pol δ
Ligase I
Ligase IV
ATM
MRN complex
RPA
BRCA2/FANCD
RAD51, FANCF
Pol δ
Pol ε
Ligase I
KU70, KU80
DNA PKs
Artemis
XRCC4-XLF
Pol μ
Ligase IV

Double Strand Break (DSB)

- The most deleterious form of DNA damage
- Generated by
  - IR radiation
  - Free radicals
  - Topoisomerase II inhibitor
  - VDJ recombination
  - Meiotic recombination
- Repaired by two major pathways
  - Homologous recombination (HR)
  - Nonhomologous end-joining (NHEJ)

Double Strand Break (DSB)

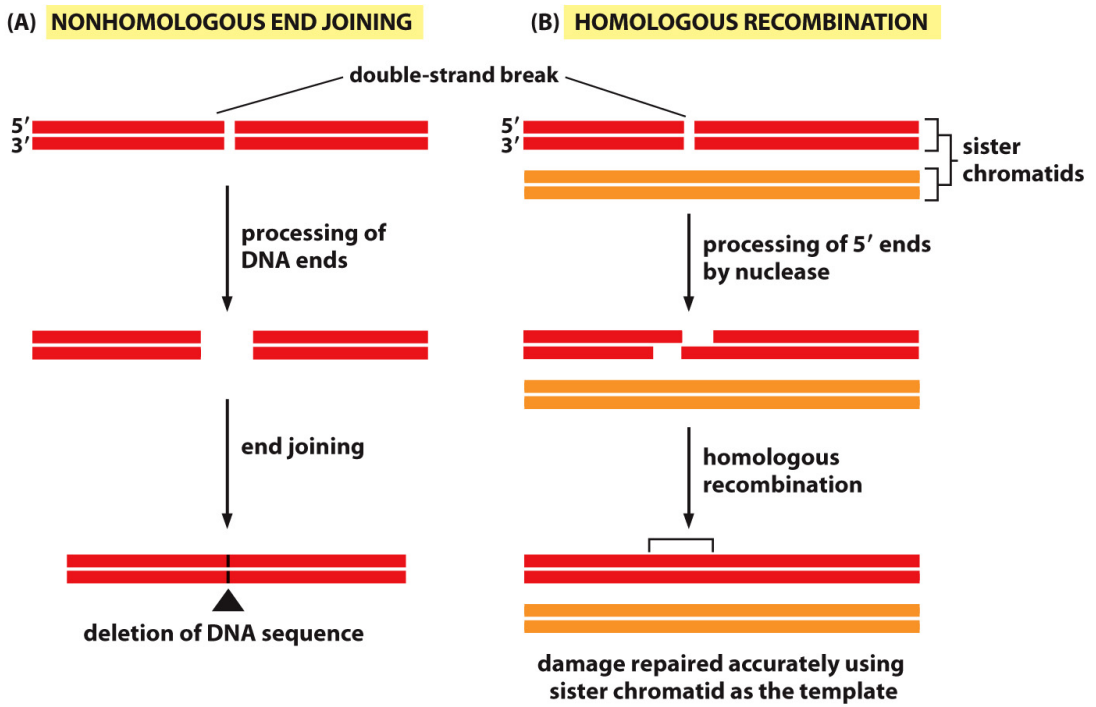
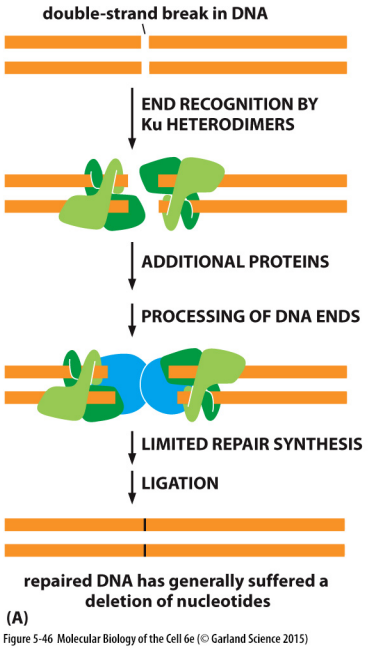


Figure 5-45 Molecular Biology of the Cell 6e (© Garland Science 2015)

Nonhomologous end-joining



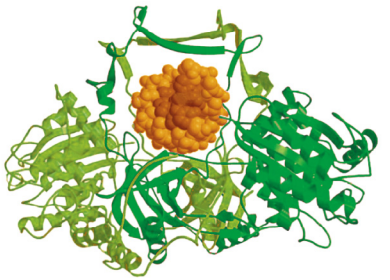


Figure 5-46 Molecular Biology of the Cell 6e (© Garland Science 2015)

Homologous recombination

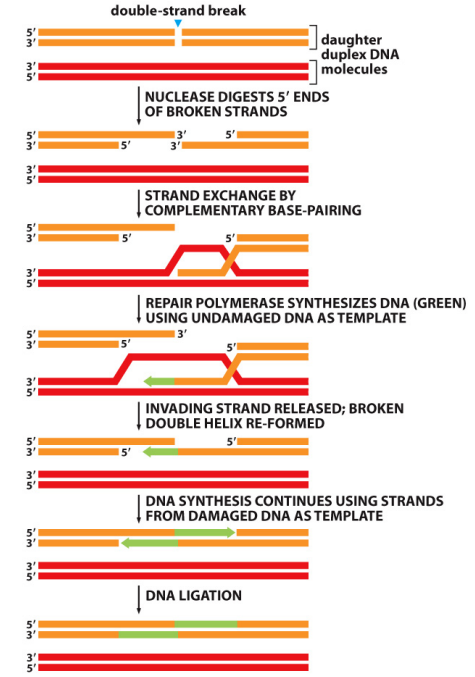


Figure 5-48 Molecular Biology of the Cell 6e (© Garland Science 2015)

Diseases Due to Defects in DNA Repair

TABLE 5–2 Some Inherited Human Syndromes with Defects in DNA Repair

Name	Phenotype	Enzyme or process affected
MSH2, 3, 6, MLH1, PMS2	Colon cancer	Mismatch repair
Xeroderma pigmentosum (XP) groups A–G	Skin cancer, UV sensitivity, neurological abnormalities	Nucleotide excision repair
Cockayne syndrome	UV sensitivity; developmental abnormalities	Coupling of nucleotide excision repair to transcription
XP variant	UV sensitivity, skin cancer	Translesion synthesis by DNA polymerase ν
Ataxia telangiectasia (AT)	Leukemia, lymphoma, γ-ray sensitivity, genome instability	ATM protein, a protein kinase activated by double-strand breaks
BRCA1	Breast and ovarian cancer	Repair by homologous recombination
BRCA2	Breast, ovarian, and prostate cancer	Repair by homologous recombination
Werner syndrome	Premature aging, cancer at several sites, genome instability	Accessory 3′-exonuclease and DNA helicase used in repair
Bloom syndrome	Cancer at several sites, stunted growth, genome instability	DNA helicase needed for recombination
Fanconi anemia groups A–G	Congenital abnormalities, leukemia, genome instability	DNA interstrand cross-link repair
46 BR patient	Hypersensitivity to DNA-damaging agents, genome instability	DNA ligase I

Table 5-2 Molecular Biology of the Cell 6e (© Garland Science 2015)

Why is BRCA1/2 special?

- High prevalence in population
- Frequent benign variant

What about hereditary breast and ovarian cancer syndrome (HBOCS)

- BRCA1/2 and other genes
- Breast, ovarian cancer and other cancers
- Prevalence (between 1 in 400 to 1 in 800 people)
- Penetration rate (40-90%)

Categories of interpretation of variants

- Pathogenic
- Likely-pathogenic
- Uncertain (VUS)
- Likely-benign
- Benign

Let's guess the evidences

Famly pedigree

Segregation data (BS1, PP1)

- Caveat: linkage disequilibrium
- Penetration rate
- Difficult statistical evaluation

Population data

- 5%: benign stand alone (BA1)
- 0.5-5% (BS1)
- Wow! The first time observed variant! (Absent in population DB, PM2)

Null variant

- Frameshift, Nonsense, canonical +-1 or 2 splicing site, initiation codon
- Caveat: LOF variants at the extreme 3′ end of a gene
- Caveat: presence of multiple transcripts

Computational (in silico) data

- PolyPhen2, SIFT, MutationTaster, etc
- Mutational hot spot and/or critical and wellestablished (PM1)
- Protein length changes due to in-frame deletions/insertions and stop losses functional domain (PM4 BP3)
- Novel missense at the same position (PM5)

Other evidence

- de novo variants (PS2 PM6)
- Functional studies (PS3 BS3)
- Allelic data (BP2 PM3)

Evidences of interpretation

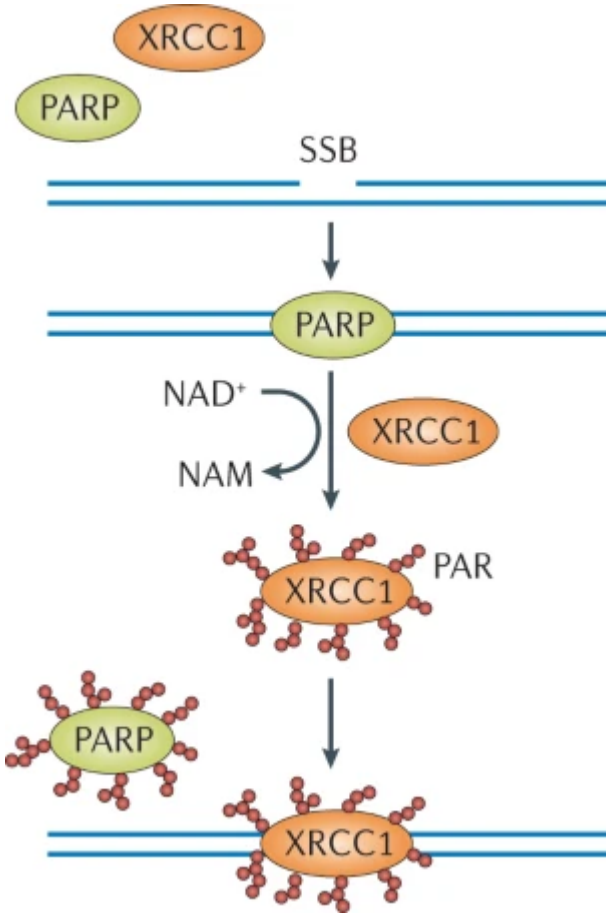
- Population data
- Computational data
- Functional data
- Segregation data
- De novo data
- Allele data
- Other databases
- Other data

Characteristics of BRCA1/2

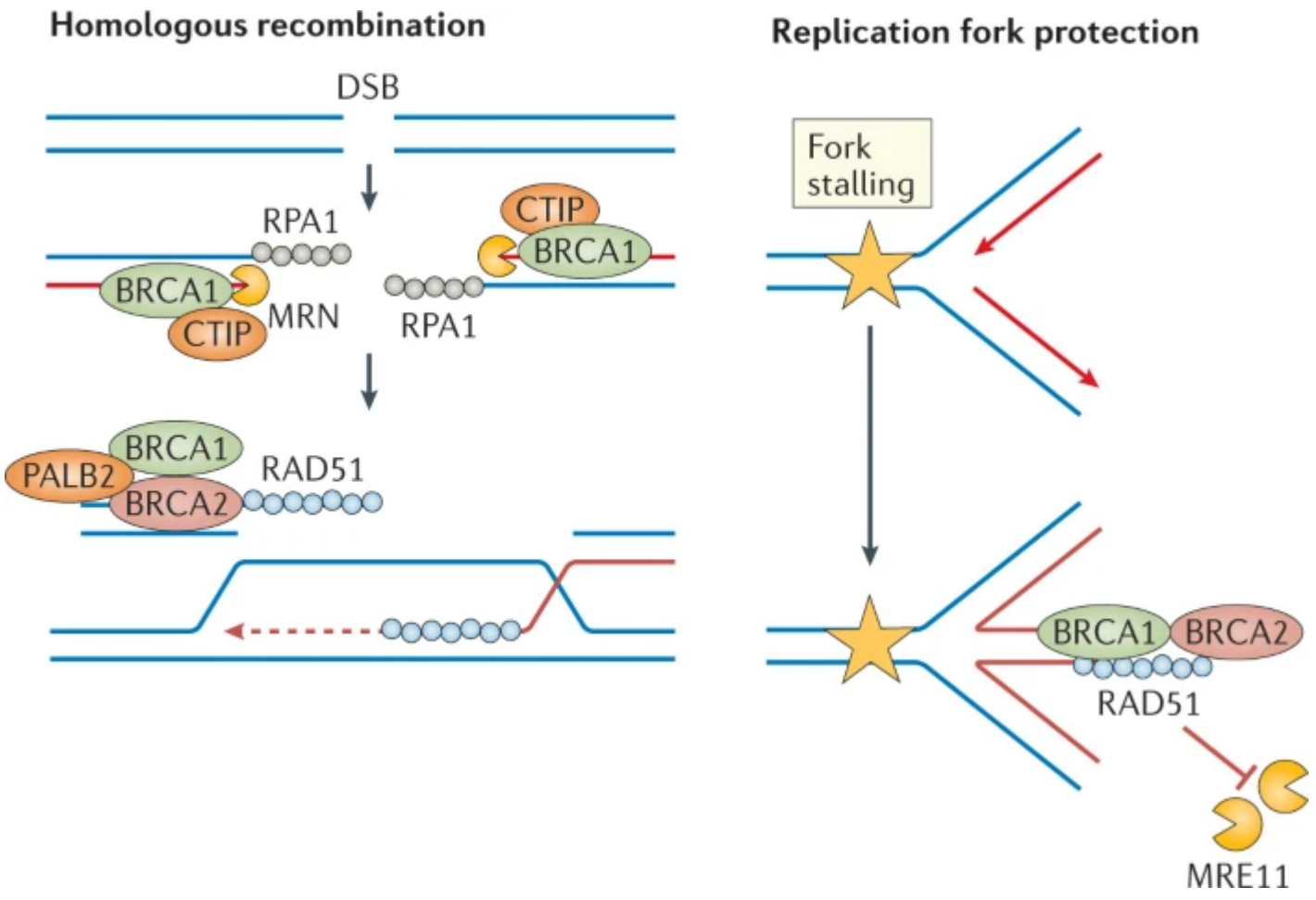
- LOF known mechanism of disease (for PVS1)
- Mode of inheritance (for PM3/BP2)
  - AD/AR (BRCA2)
- Missense pathogenic (for PP2/BP1)
  - BRCA2 1%
- Hot spot or critical/well-established functional domain (for PM1)
  - BRCA2, Helical (2479-2667), OB (2670-2799 and 3052-3190), Tower (2831-2872)

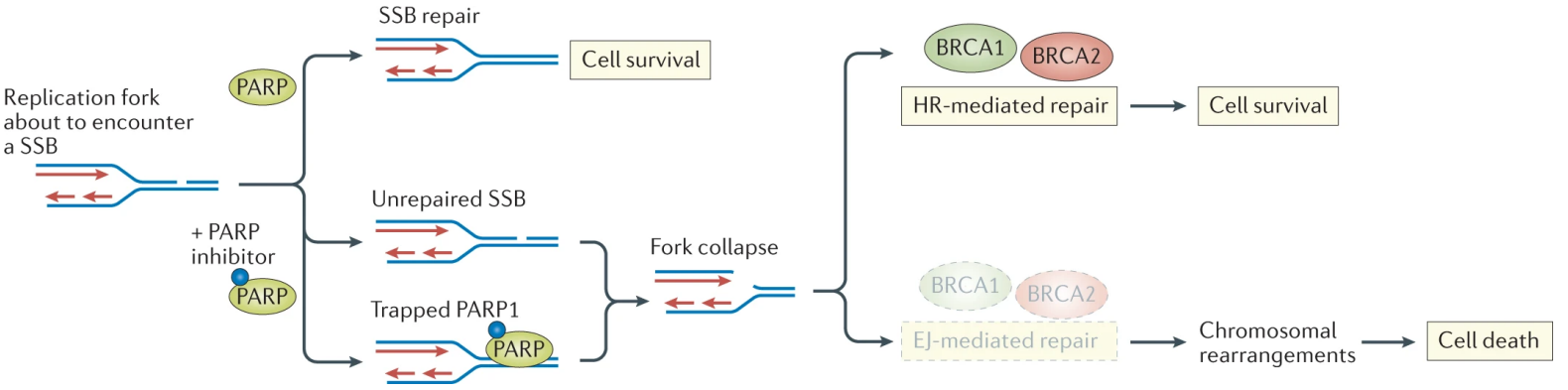
BRCA1/2 gene analysis

- BRCA1
  - p.Glu1148Argfs*7
  - c.3442del

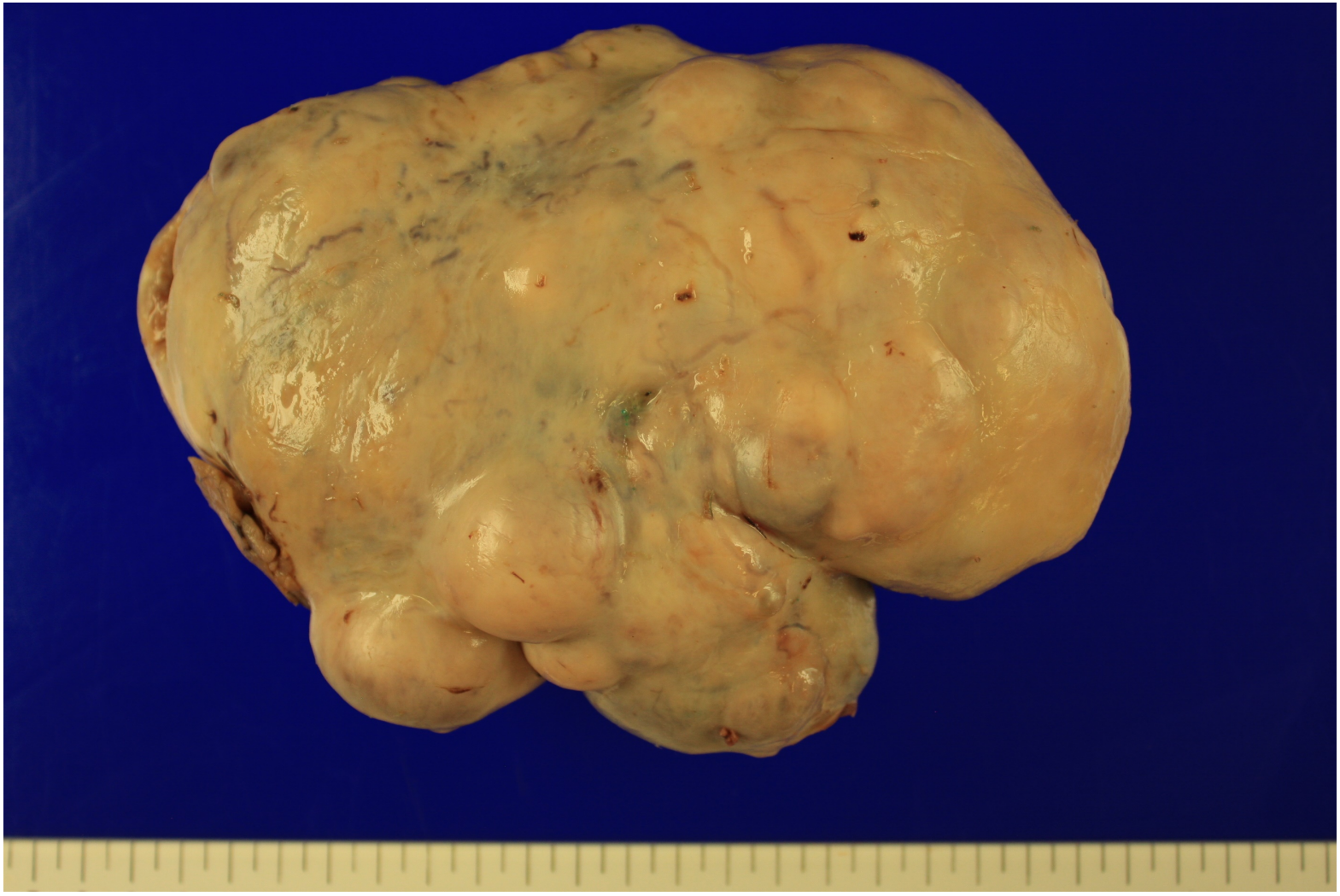


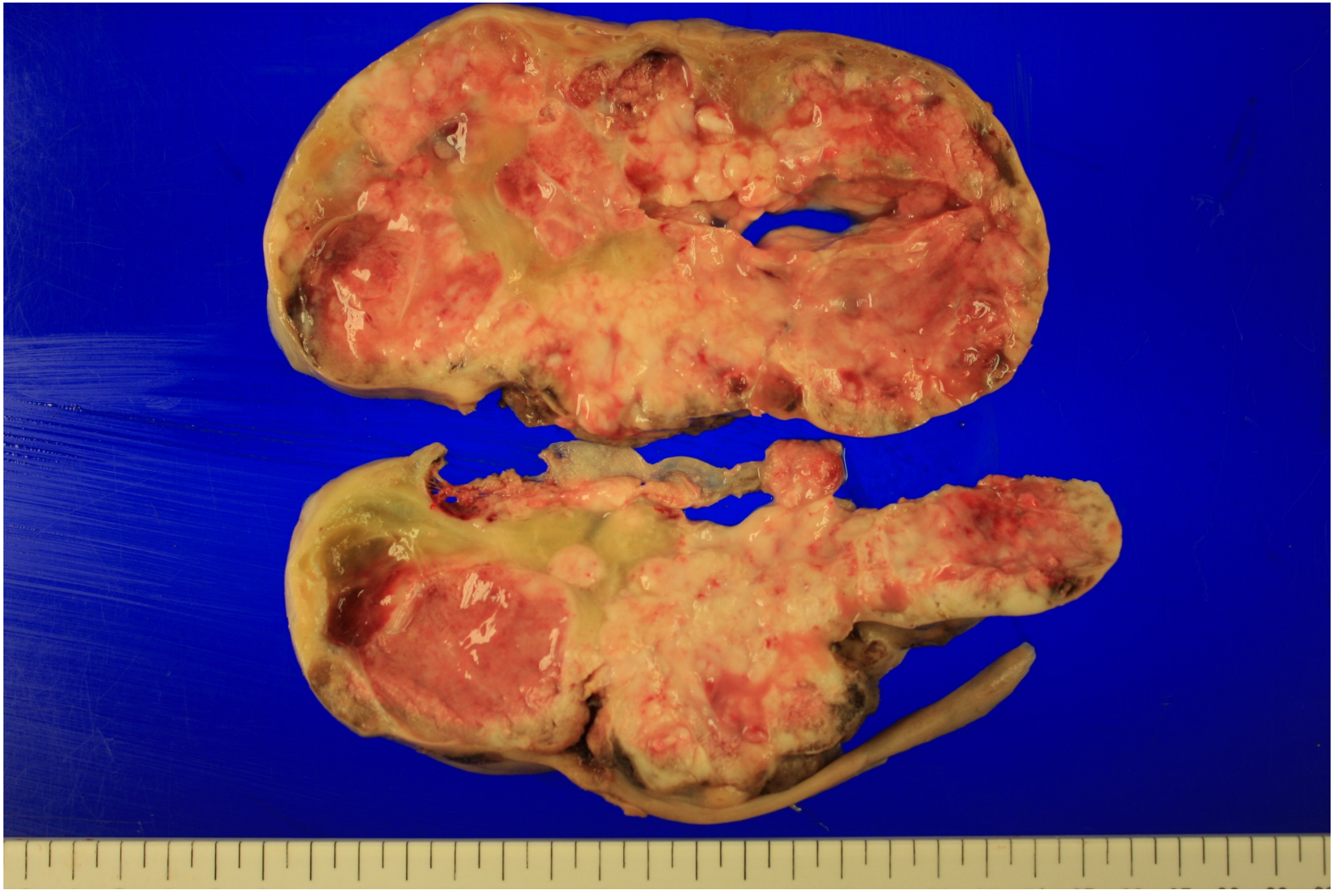
Nature Reviews Clinical Oncology volume 18, pages773–791 (2021)

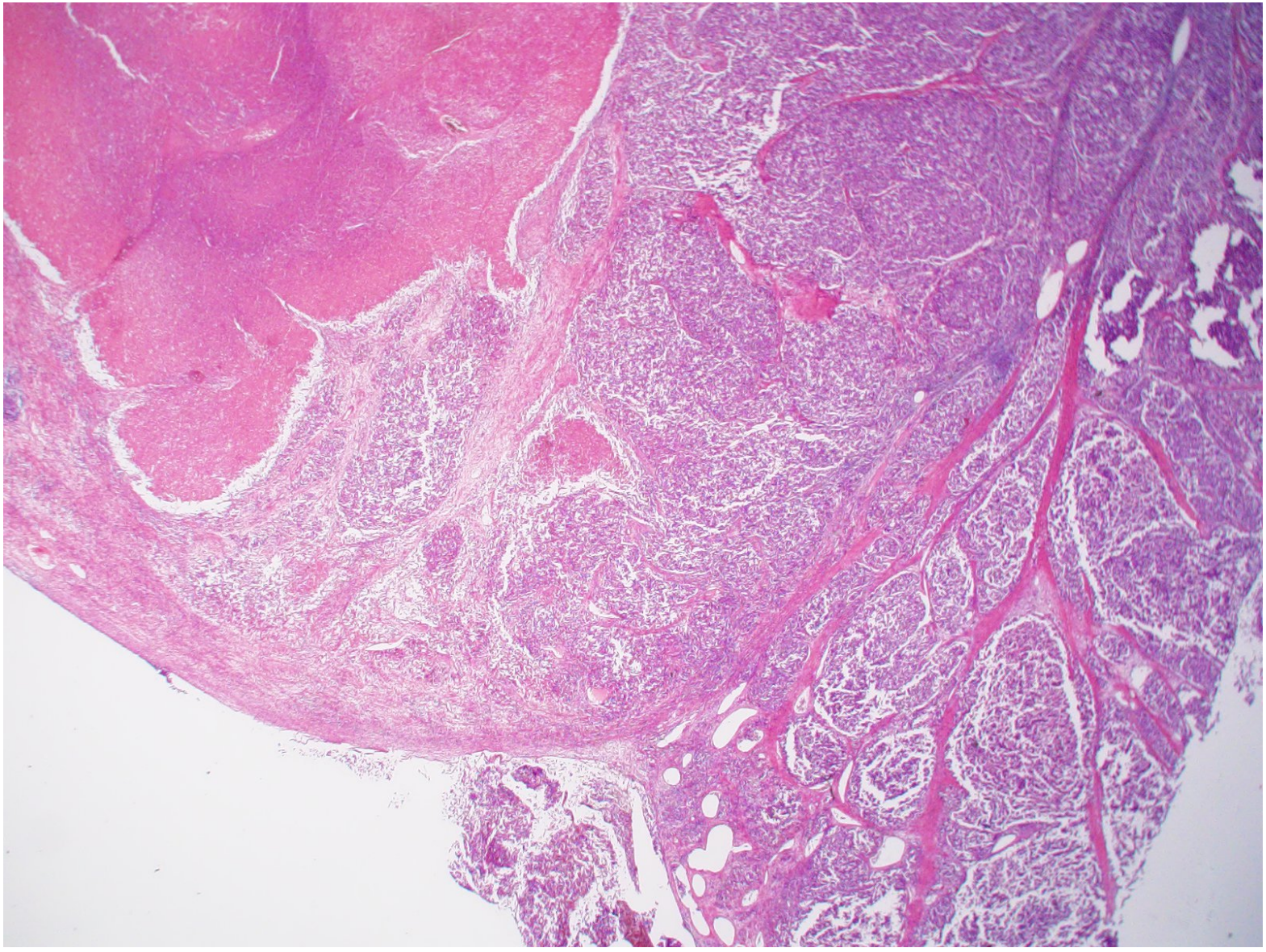

Homologous recombination
DSB
RPA1
CTIP
BRCA1
BRCA1
MRN
CTIP
RPA1
BRCA1
PALB2
RAD51
BRCA2
Replication fork protection
Fork stalling
BRCA1
BRCA2
RAD51
MRE11

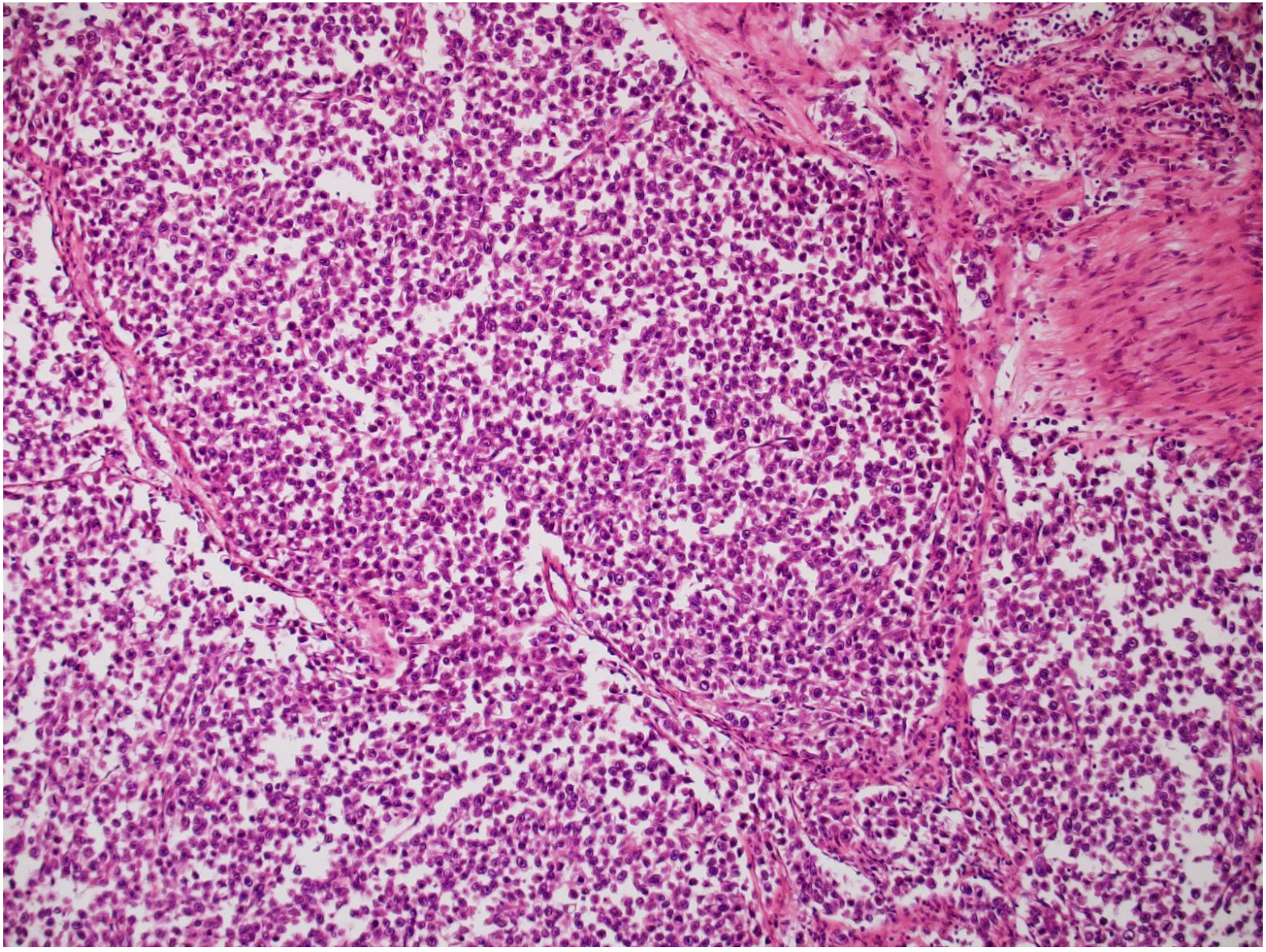

Replication fork about to encounter a SSB
PARP
SSB repair
Cell survival
+ PARP inhibitor
PARP
Unrepaired SSB
Trapped PARP1
PARP
Fork collapse
BRCA1
BRCA2
HR-mediated repair
Cell survival
BRCA1
BRCA2
EJ-mediated repair
Chromosomal rearrangements
Cell death

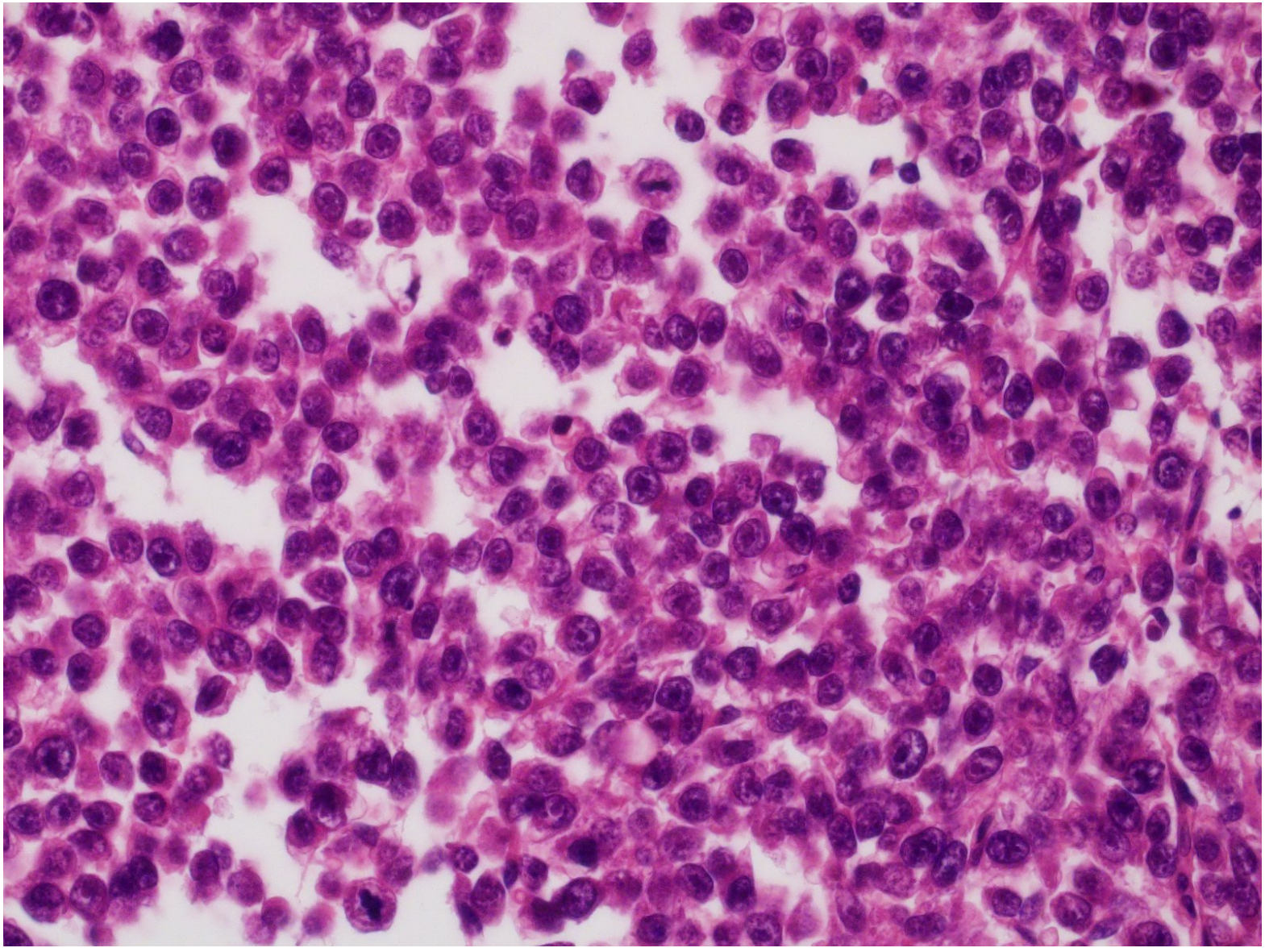
Case 2

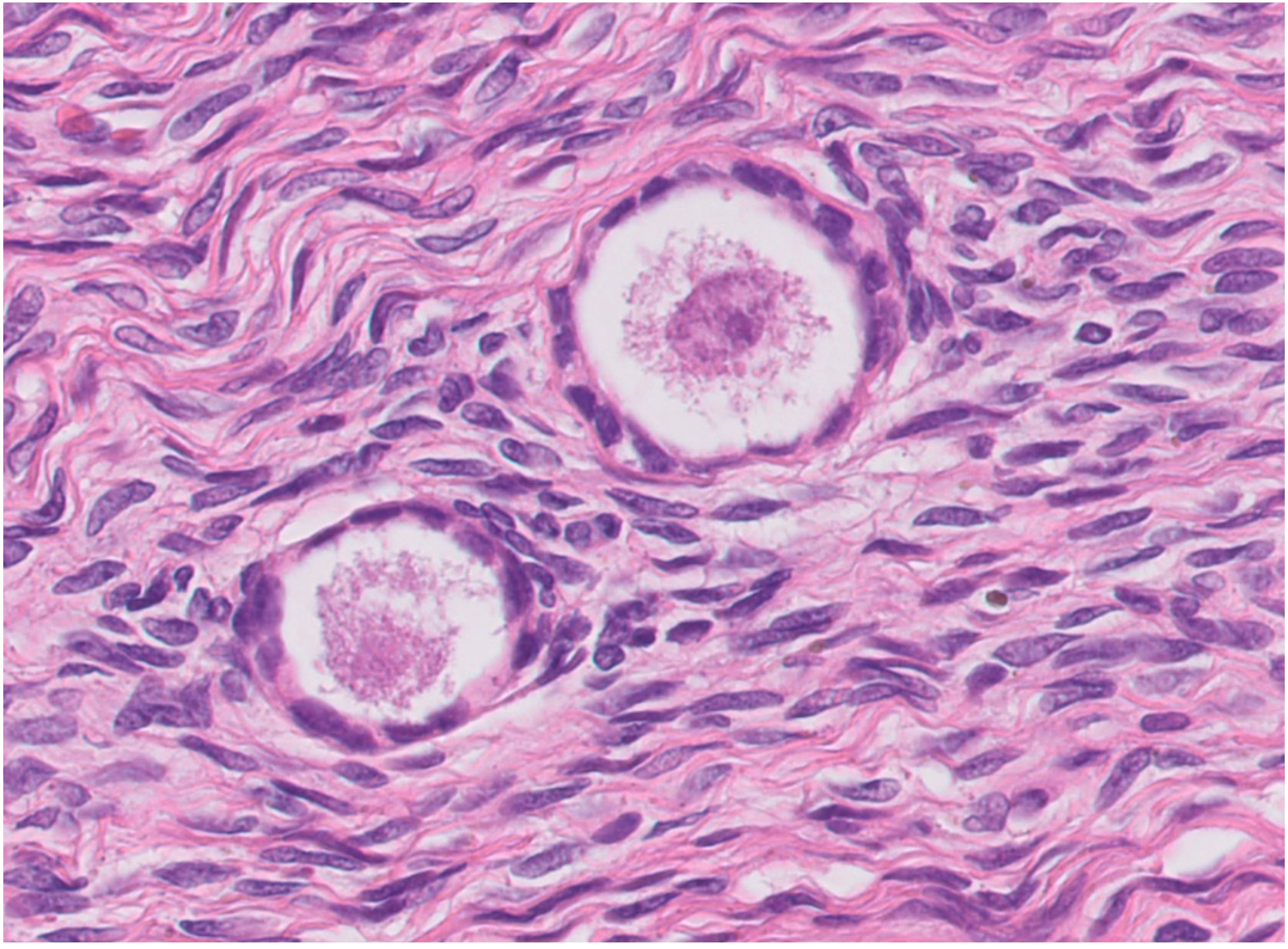


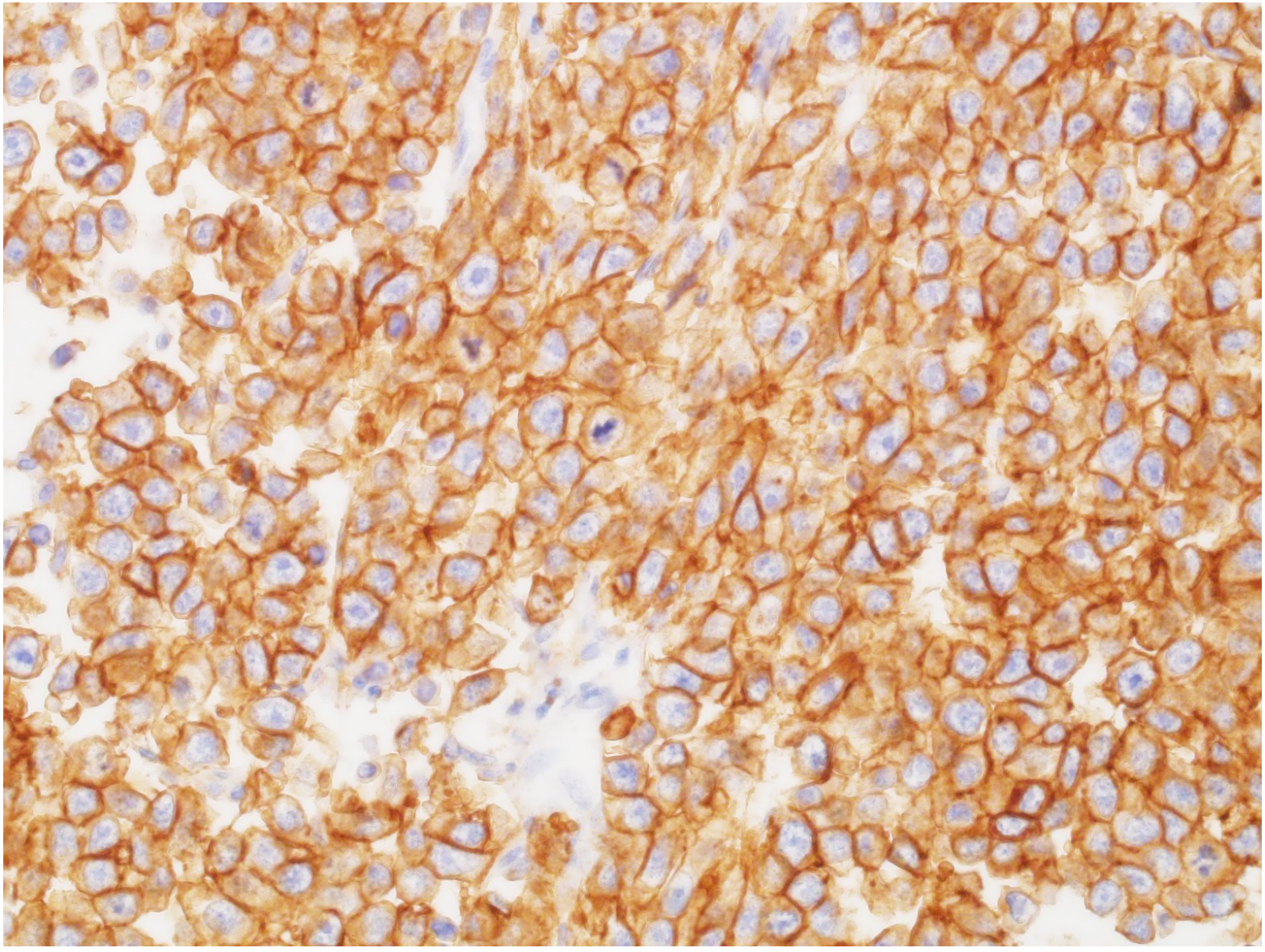






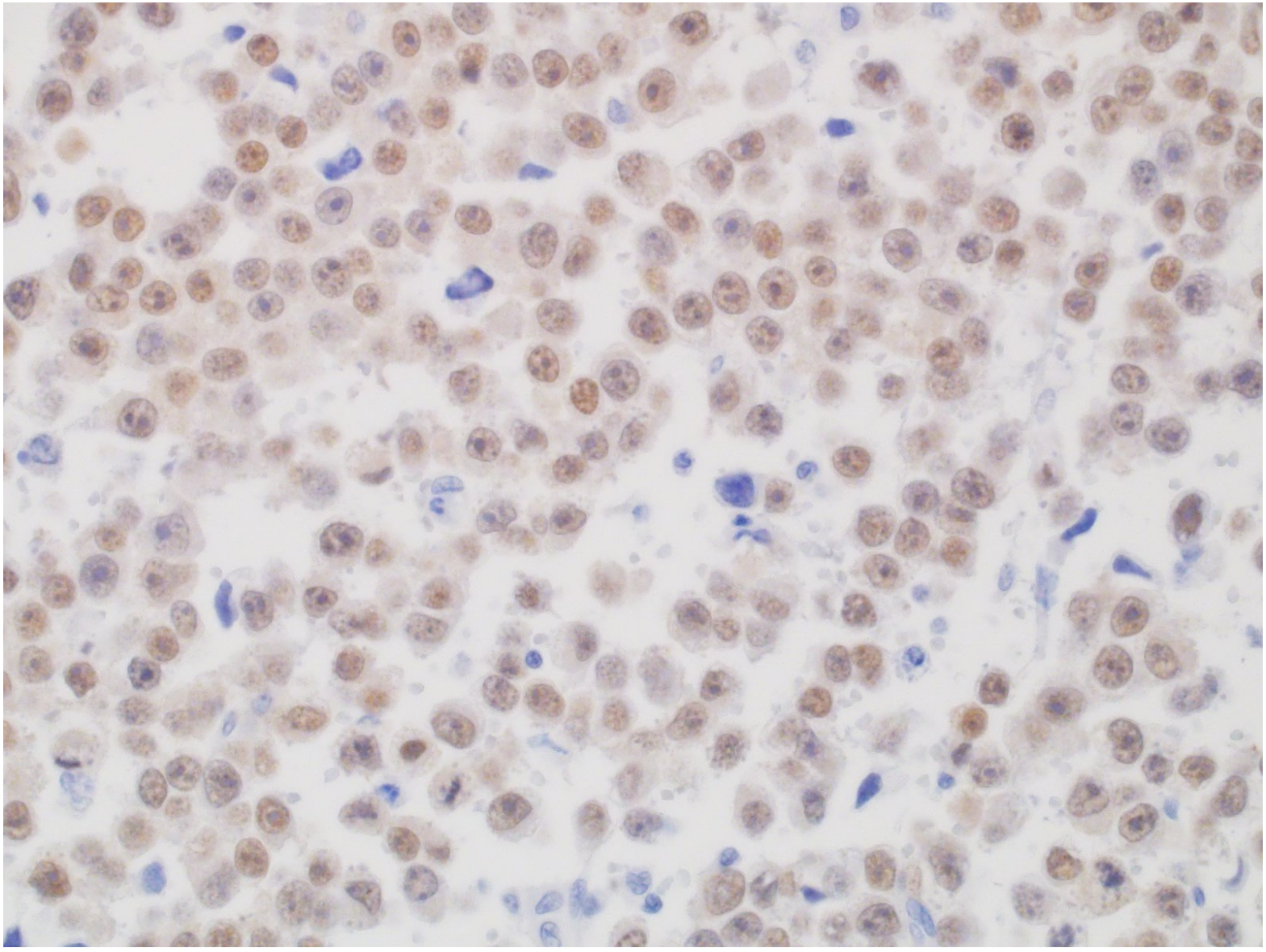






C-kit

- Platelet-derived growth factor receptor (PDGFR) family
- Cell surface receptors
- Stem cell factor ligand
- Essential in the development of melanocytes, germ cells, mast cells, erythrocytes, and interstitial cells of Cajal
- KIT mutations occur in 25%–50% of tumors, most commonly involving codon 816 of exon 17



oct3/4

- One of four transcription factors (OCT4, Sox2, Nanog and Lin28) induce pluripotency in somatic cells