PTEN hamartoma tumor syndrome (PHTS)

COWDEN SYNDROME

Malattia di Cowden o PHTS: Generalità

- La malattia di Cowden è anche definita sindrome di Cowden o PTEN hamartoma tumor syndrome (PHTS)
- Originariamente descritta nel 1963, la malattia di Cowden prende il nome dalla famiglia in cui è stata descritta per la prima volta.

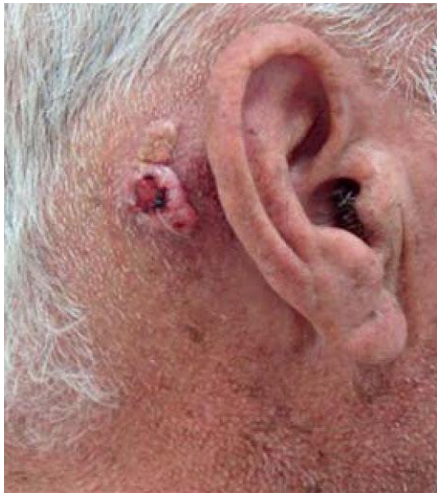
- È associata a mutazioni nel gene *PTEN* (phosphatase and tensin homolog) gene

- sindromi tumorali caratterizzate da mutazioni di PTEN comprendono:
  - Cowden disease
  - Bannayan-Riley-Ruvulcaba syndrome (BRRS)
  - Proteus syndrome
  - Proteus-like syndrome

Caratteristiche Cliniche non maligne

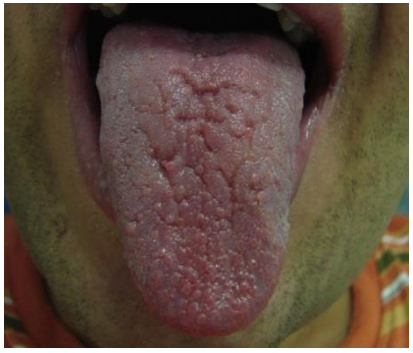
- Circa il 99% degli individui con sindrome di Cowden sviluppa escrescenze benigne sulla pelle e / o in bocca entro i 20 anni.

macrocephaly

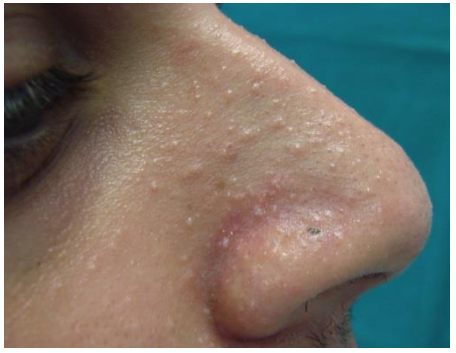


trichilemmoma

- Gli individui affetti di solito presentano macrocefalia, tumori benigni del follicolo pilifero (trichilemmomi) e papule papillomatose



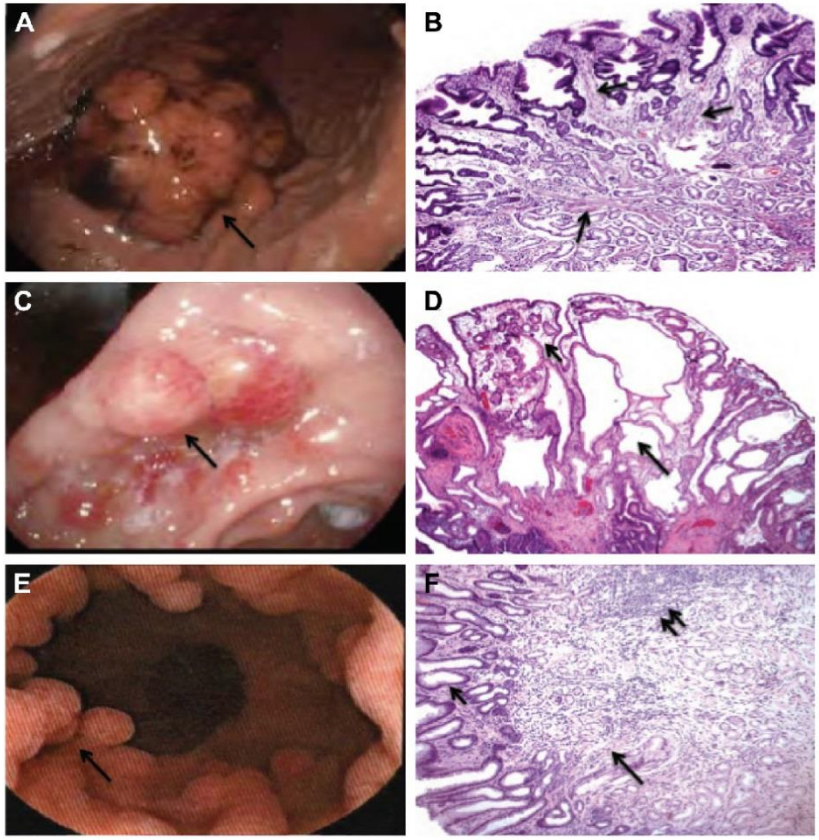
papillomatous papules



Small papules

Caratteristiche Cliniche: polipi amartomatosi

- La maggior parte delle persone con sindrome di Cowden sviluppa polipi amartomatosi lungo il rivestimento interno del tratto gastrointestinale.
- Polipi amartomatosi: crescita simile a un tumore; fatti da tessuti maturi; ghiandole cistiche dilatate anziché aumento del numero di cellule epiteliali



From: M. Vyas et al. Clinical medicine insights, 2016

Sindromi amartomatose umane

	Genes	Hallmark features	Cancer by site	Approx. mutation detection rate (%)
Juvenile polyposis syndrome	*SMAD4, BMPR1A*	Multiple GI-polyps, epistaxis,* telangiectasia*	Colon, rectum and stomach	60% [2]
PTEN-hamartoma syndrome: Cowden Syndrome	*PTEN*	Lhermitte-Duclos disease, trichilemmoma, skin hamartoma, macrocephaly,	Breast, thyroid, uterus, colon	Up to 80% [6]
PTEN-hamartoma syndrome: Bannayan-Riley-Ruvalcaba	*PTEN*	Macrocephaly, lipomatosis, pigmented macules of the glans penis	As above	60% [7]
Peutz-Jeghers syndrome	*STK11 (LKB1)*	Mucocutanous melanosis and polyposis of the GI-tract	Colon, stomach, breast, pancreas (cervix, ovarian)	80%-94% [8]
Hereditary mixed polyposis syndrome	*(BMPR1A, GREM1)*	Atypical polyposis with juvenile polyps, adenomas, hyperplastic and inflammatory	Colon and rectum	Unknown

*In *SMAD4* mutation carriers.

Other syndromes with hamartomatous lesions

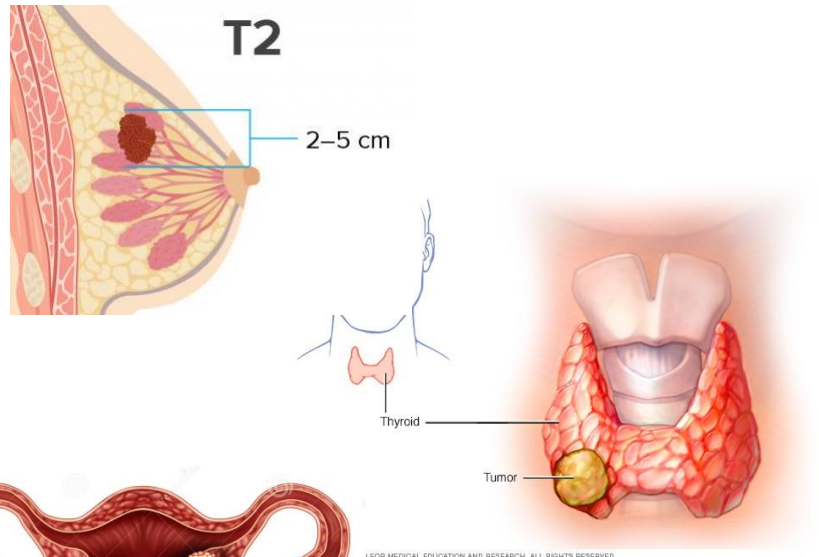
	Clinical hallmarks	Gene	Cancer
Gorlin syndrome	Keratocysts of the jaw, hyperkeratosis of palm and soles, basal cell carcinomas, skeleton abnormalities, macrocephaly, frontal bossing	*PTCH1*	Basal cell carcinomas, medullablastoma
Multiple endocrine neoplasia type 2B	Mucosal neuromas of the lips an tongue, medullated corneal nerve fibers, distinctive facies with enlarged lips and tongue, an asthenic "marfarnoid habitus, and medullary thyroid cancer.	*RET*	Medullary thyroid cancer, pheochromocytoma
Neurofibromatosis type 1	Café au lait spots, axillary and inguinal freckling, and neurofibromas.	*NF1*	Optic gliomas, malignant peripherical nerve sheath tumours, breast
Birt-Hogg-Dubé	Skin fibrofolliculomas, spontaneous pneumothorax	*FLCN*	Renal

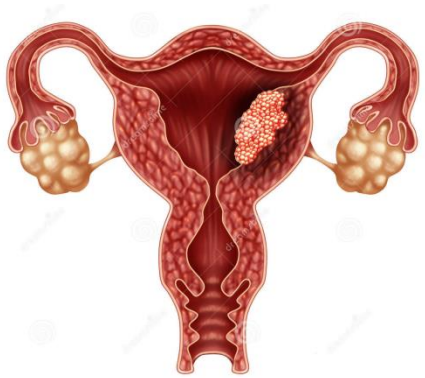
From: Jelsih AM. Orphanet Journal of Rare Diseases **9**: 101 (2014)

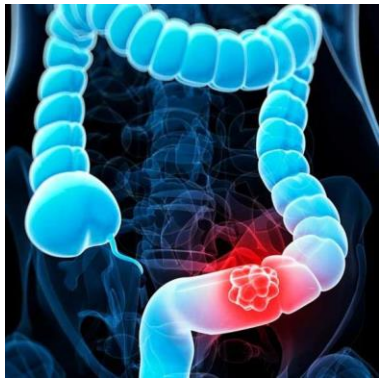
Caratteristiche Cliniche: rischio di cancro

- Il rischio di carcinoma mammario è dell'85%, con un'età media di diagnosi compresa tra 38 e 46 anni.
- Il rischio di carcinoma tiroideo (di solito follicolare) è del 35% circa.
- Il rischio di carcinoma dell'endometrio è del 28% circa.

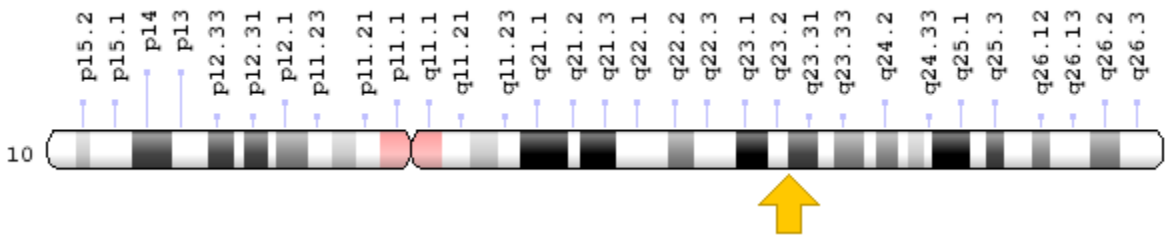
- altri tipi di tumori maligni, come carcinoma del colon, carcinoma renale e melanoma, possono verificarsi in pazienti con malattia di Cowden

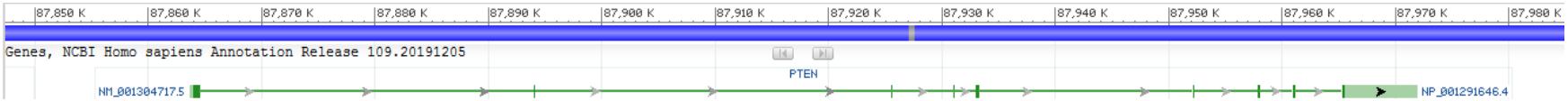






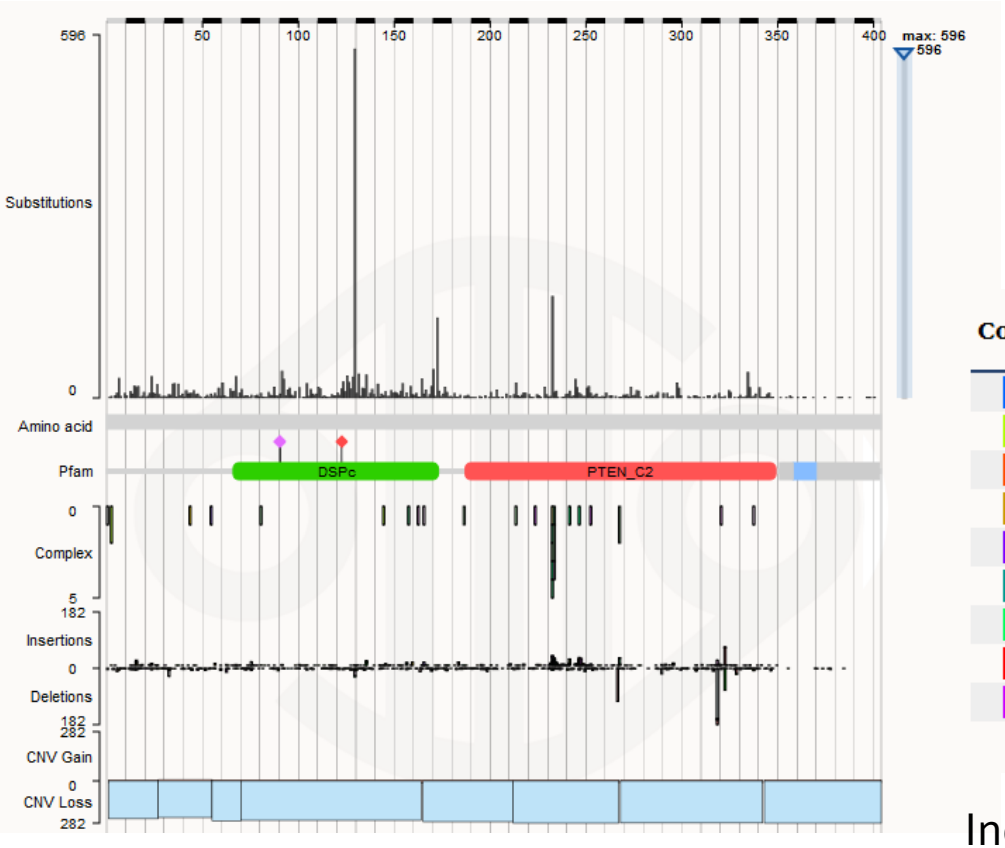
Fisiopatologia: il gene *PTEN*





Il gene PTEN si estende per oltre 120 kb nel cromosoma 10q24
Comprende 9 esoni.
Il gene codifica per una proteina di 403 aminoacidi

PTEN mutazioni



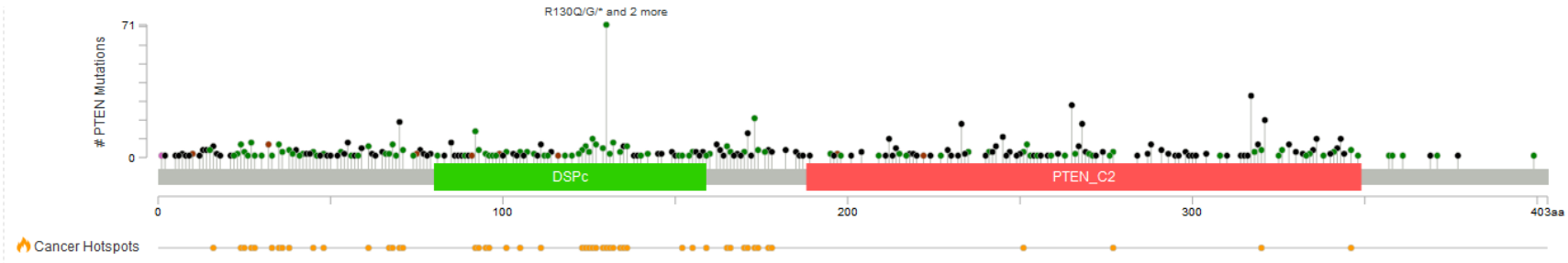
Varianti patogene germinali sono state trovate in tutto il gene PTEN (ad eccezione dell'esone 9)

Colour	Mutation type	Number of samples (%)
	Nonsense substitution	924 (16.64%)
	Missense substitution	2121 (38.20%)
	Synonymous substitution	59 (1.06%)
	Inframe insertion	25 (0.45%)
	Frameshift insertion	555 (10.00%)
	Inframe deletion	125 (2.25%)
	Frameshift deletion	911 (16.41%)
	Complex mutation	29 (0.52%)
	Other	634 (11.42%)
	Total unique samples	5552

From COSMIC Database

Include varianti missenso, nonsenso e splice-site, piccole delezioni, inserzioni e grandi delezioni.

PTEN mutazioni



PTEN

RefSeq: NM_000314
Ensembl: ENST00000371953
CCDS: CCDS31238
UniProt: PTEN_HUMAN

Somatic Mutation Frequency 5.8%

367 Missense 585 Truncating
29 Inframe 8 Other

From CBIO Portal database

- Più di 150 varianti patogene uniche sono attualmente elencate nel database di mutazione del gene umano.
- Il 40% delle varianti patogene si trova nell'esone 5, che codifica il dominio fosfatasico [Eng 2003].

PHTS: *PTEN* mutazioni

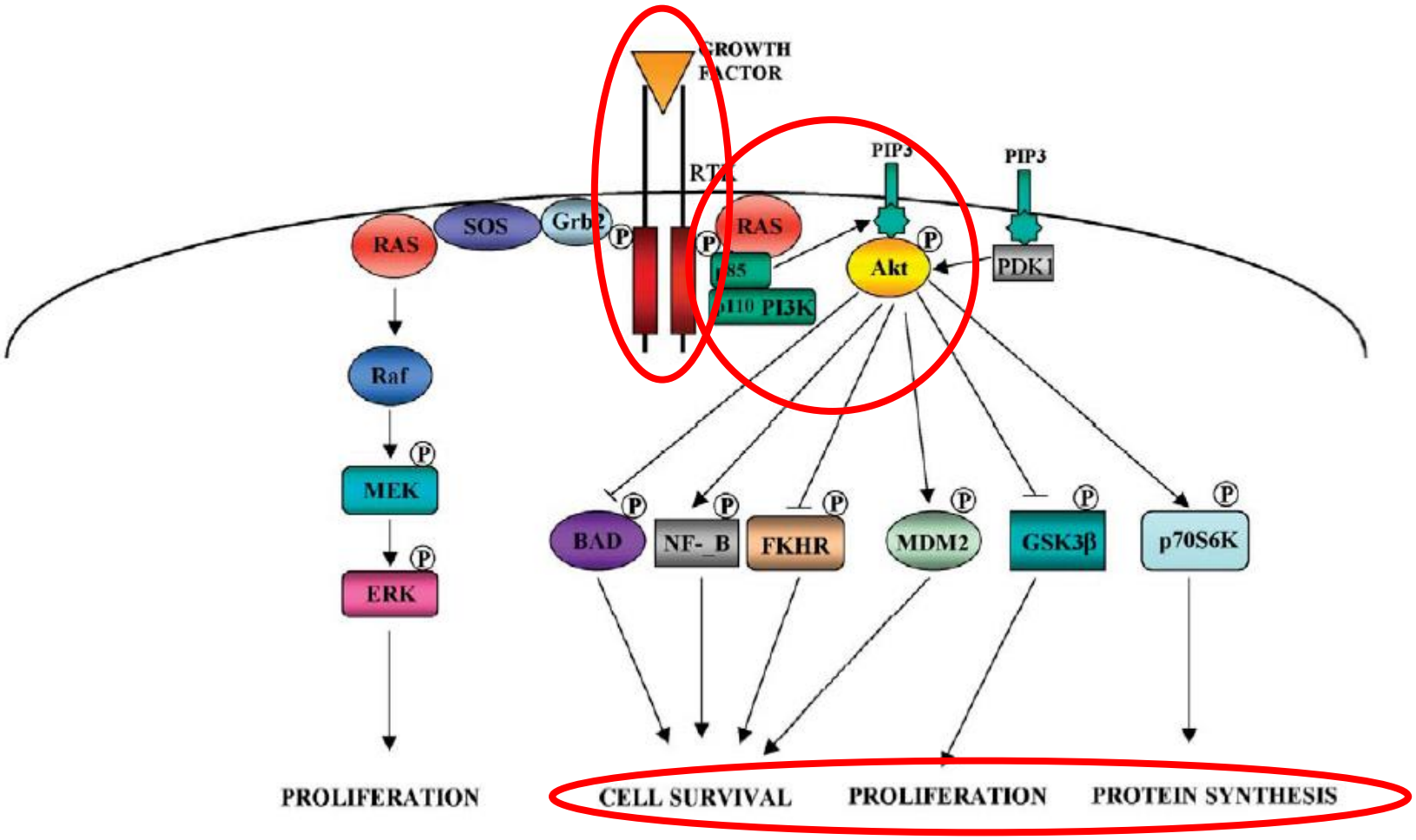
Gene [1]	Test Method	Proportion of Probands by Phenotype with a Pathogenic Variant Detectable by This Method			
		CS	BRRS	PLS	PS
PTEN	Sequence analysis of coding region [2]	25%-80%	60%	50% [3]	20%
	Deletion/duplication analysis [4]	See footnote 5	11% [6]	Unknown	Unknown
	Sequence analysis of promoter region [2]	10% [7]	See footnote 5	Unknown	Unknown

CS = Cowden syndrome
BRRS = Bannayan-Riley-Ruvalcaba syndrome
PLS = Proteus-like syndrome
PS = *PTEN*-related Proteus syndrome

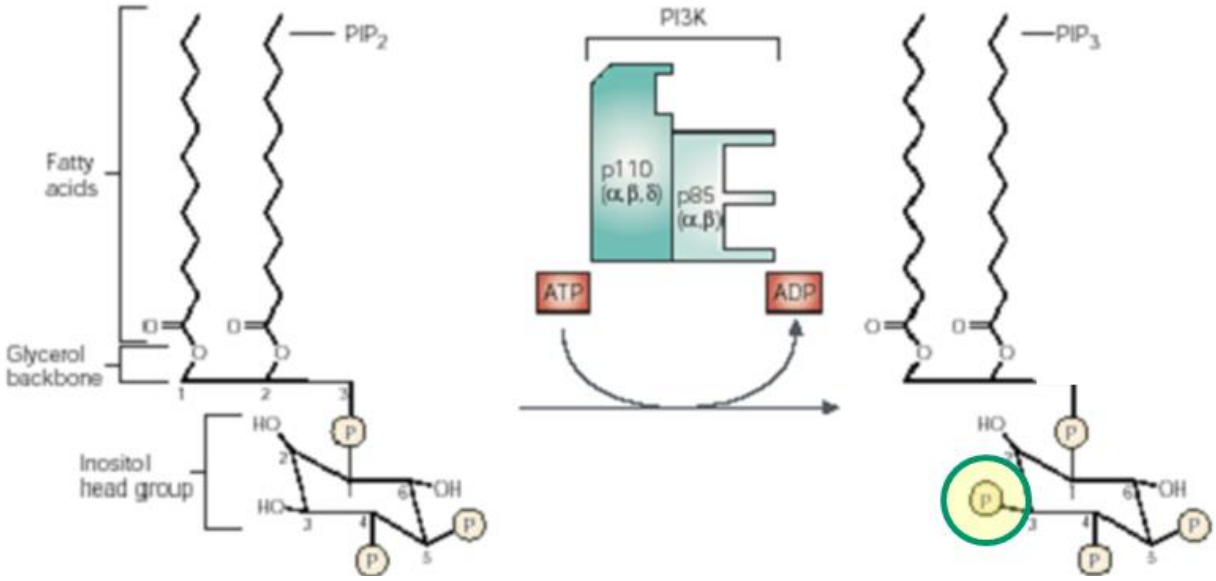
Circa il 10% degli individui con CS che non hanno una variante patogena rilevata nella sequenza codificante presenta varianti patogene germinali nel promotore PTEN [Zhou et al 2003b].

Al contrario, il 10% degli individui con BRRS che non hanno una variante patogena identificabile del PTEN sull'analisi della sequenza presenta ampie delezioni all'interno o che comprendono il PTEN [Zhou et al 2003b].

PTEN and the PI3K Pathway



PI3K converte PIP2 in PIP3 e promuove attività di AKT

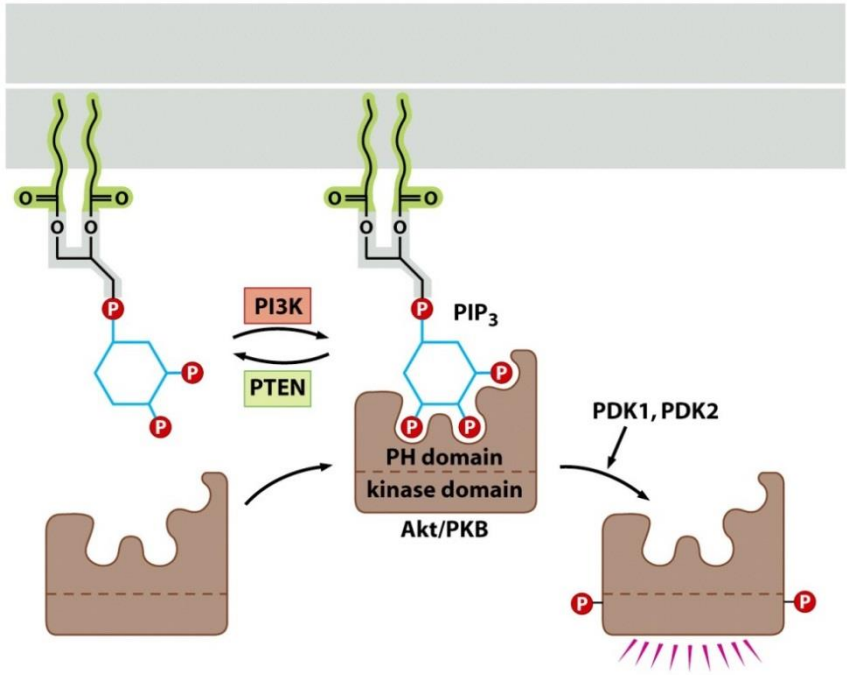


Il legame di PI3K con recettori tirosin chinasi o Ras fa sì che PI3K si associ strettamente alla membrana plasmatica, dove si trova il suo substrato PIP2 che viene convertito in PIP3

PIP3 è un sito di aggancio di AKT

PIP3 costituisce un sito di legame per proteine citoplasmatiche contenenti domini pleckstrin (PH).

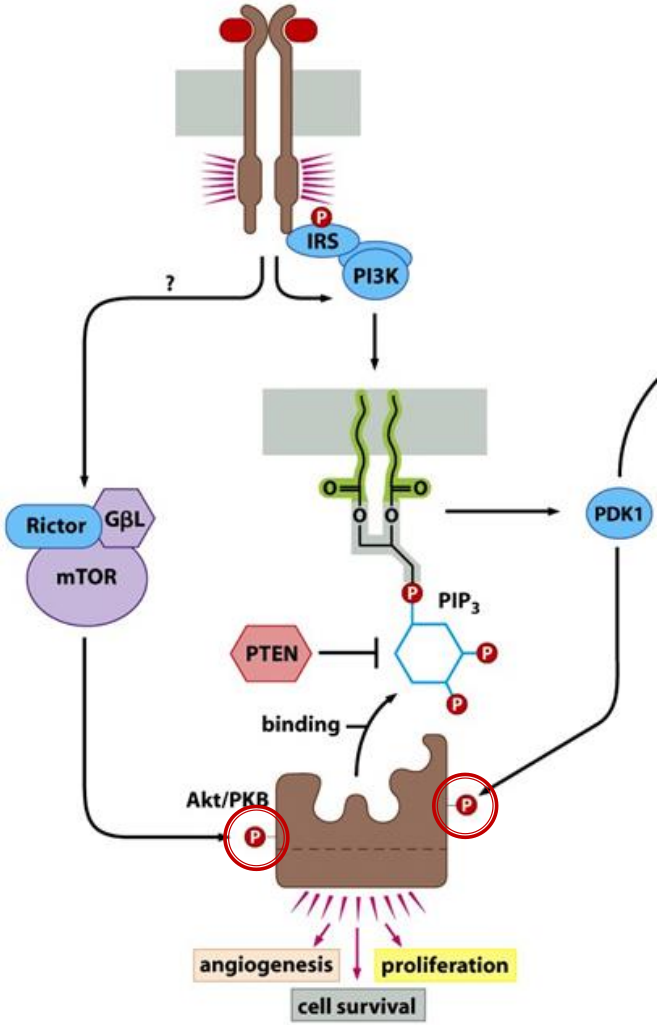
Il più importante è la chinasi AKT.



AKT attivato da fosforilazione

PIP3 costituisce un sito di legame per proteine citoplasmatiche contenenti domini pleckstrin (PH). Il più importante è la chinasi AKT.

Legandosi alla membrana plasmatica, AKT è attivato tramite fosforilazione da due chinasi (PDK1 e mTOR)



AKT promuove sopravvivenza proliferazione e sintesi proteica

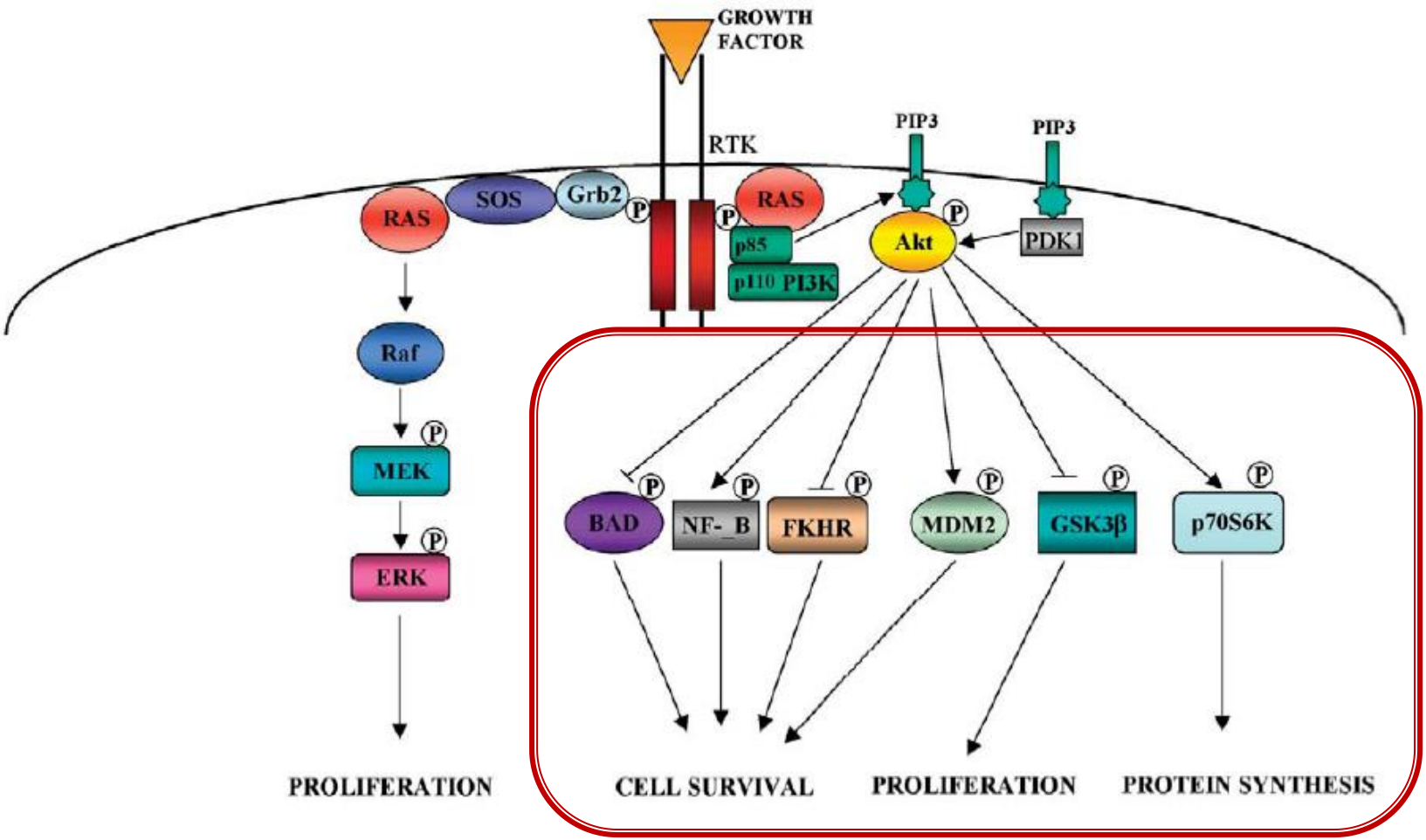
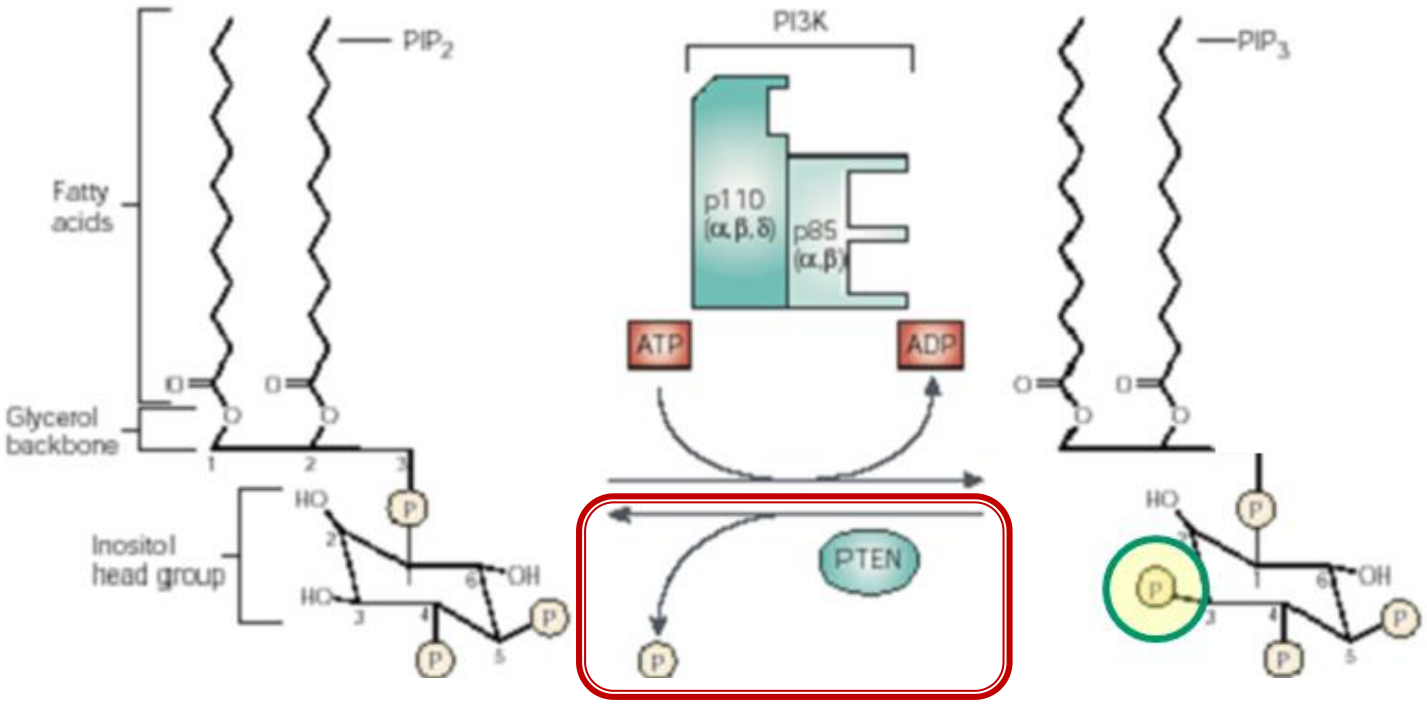


Table 6.3 Effects of Akt/PKB on survival, proliferation, and cell growth

Biological effect	Substrate of Akt/PKB	Functional consequence
Anti-apoptotic		
	Bad (pro-apoptotic)[a]	inhibition
	caspase-9 (pro-apoptotic)[b]	inhibition
	IκB kinase (anti-apoptotic)[c]	activation
	FOXO1 TF (pro-apoptotic)[d]	inhibition
	Mdm2 (anti-apoptotic)[e]	activation
Proliferative		
	GSK-3β (anti-proliferative)[f]	inhibition
	FOXO4 (anti-proliferative)[g]	inhibition
	$p21^{Cip1}$ (anti-proliferative)[h]	inhibition
Growth		
	Tsc2 (anti-growth)[i]	inhibition

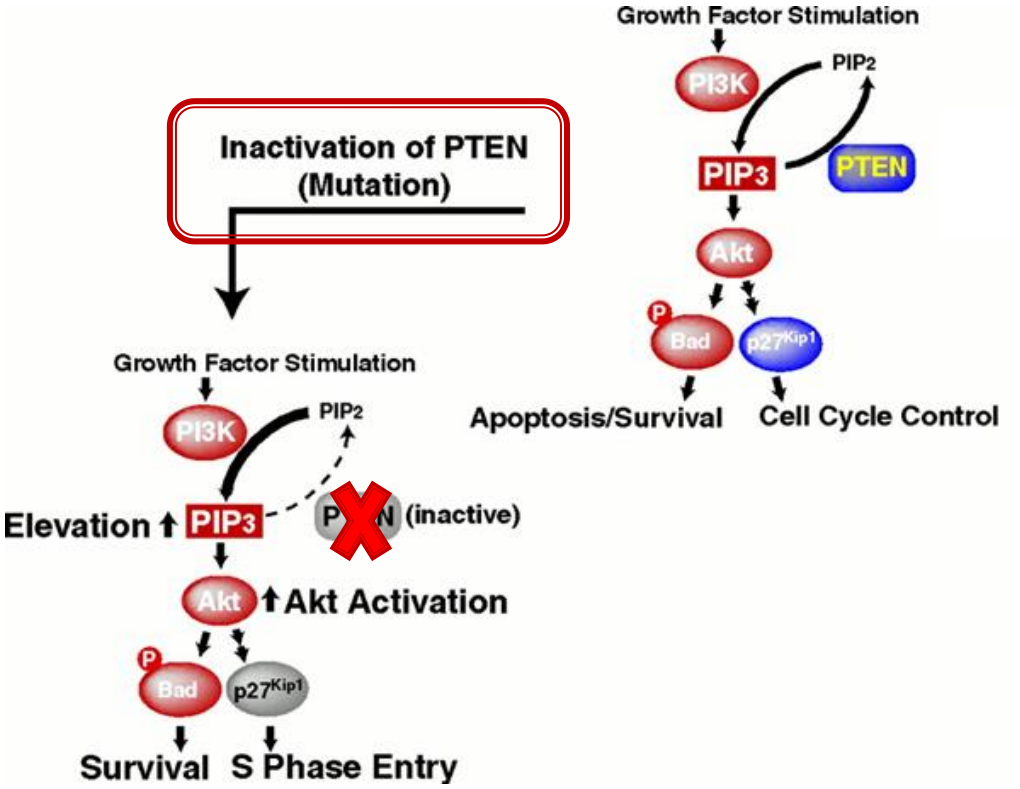
[a]Bad is an antagonist of Bcl-X; both are members of the Bcl-2 family of proteins controlling pores in the mitochondrial membrane (Section 9.13).
[b]Caspase-9 is a component of the protease cascade that effects the apoptotic program (Section 9.13).
[c]IκB kinase, usually indicated as IKK, is phosphorylated and activated by Akt/PKB (Section 6.12).
[d]Phosphorylation of the forkhead (FOXO1, previously called FKHR) TF prevents its nuclear translocation and subsequent activation of pro-apoptotic genes.
[e]Mdm2, once phosphorylated by Akt/PKB, is activated and proceeds to trigger the destruction of p53 (Section 9.7).
[f]Akt/PKB phosphorylates and inactivates glycogen synthase kinase 3β (GSK-3β) activity, which is normally responsible for phosphorylating cyclin D1 (Section 8.5), causing its degradation.
[g]FOXO4 (formerly called AFX) induces expression of the CDK-inhibitor $p27^{Kip1}$ (Section 8.4) gene and some pro-apoptotic genes; once phosphorylated by Akt/PKB, FOXO4 is exported from the nucleus.
[h]$p21^{Cip1}$ is a CDK inhibitor like $p27^{Kip1}$ (Section 8.4). Phosphorylation by Akt/PKB causes it to exit the nucleus. Once in the cytoplasm, the resulting phosphorylated $p21^{Cip1}$ has been reported to act as a caspase inhibitor, thereby acquiring anti-apoptotic functions (Section 9.13).
[i]Phosphorylation of Tsc2 by Akt/PKB causes the Tsc1/Tsc2 complex to dissociate, allowing activation of mTOR, which proceeds to up-regulate protein synthesis (Section 16.15).

PTEN regola negativamente PI3K-AKT activity

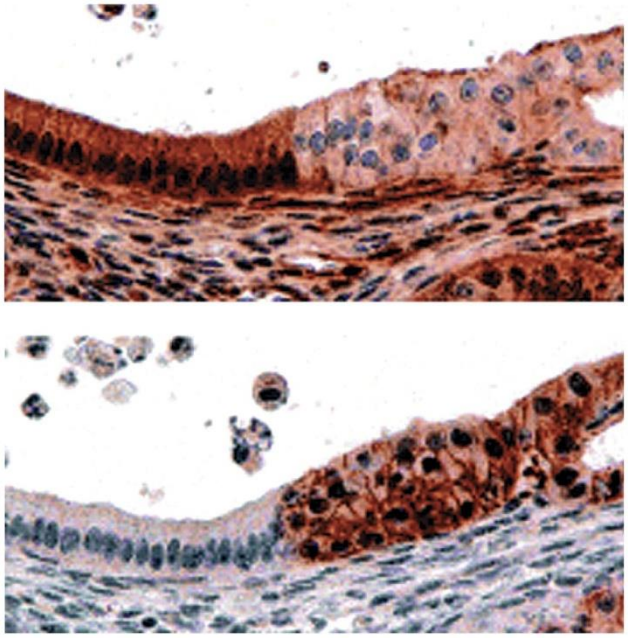


PTEN è una fosfatasi che converte PIP3 in PIP2, inibendo così l'attività del pathway PI3K-AKT

Inattivazione di PTEN consente a PI3K-AKT di rimanere attiva



Uterine epithelial cells



PTEN

Phospho AKT

In assenza di PTEN, la via PI3K-AKT rimane stabilmente attiva

Alterazioni di PI3K, AKT e PTEN nei tumori sporadici umani

Table 1 | **Evidence of PI3K-signalling deregulation in human malignancies**

Cancer type	Type of alteration	References
Glioblastoma	*PTEN* mutation	133
Ovarian	Allelic imbalance and mutations of *PTEN* gene	134
	Elevated AKT1 kinase activity	135
	AKT2 amplification and overexpression	71
	PI3K *p110α* amplification	70
	PI3K *p85α* mutation	74
Breast	Elevated AKT1 kinase activity	135
	AKT2 amplification and overexpression	71
	RSK amplification and overexpression	78,79
	Loss of heterozygosity at *PTEN* locus	136
	PI3K and AKT2 overactivation	137
Endometrial	*PTEN* mutation	138
	PTEN silencing	139
Hepatocellular carcinoma	*PTEN* mutation	140
Melanoma	*PTEN* mutation	141
	PTEN silencing	142
Digestive tract	Aberrant *PTEN* transcripts	143
	PI3K *p85α* mutation	74
Lung	PTEN inactivation	144
Renal-cell carcinoma	*PTEN* mutations	145
Thyroid	*PTEN* mutations	146–148
	AKT overexpression and overactivation	149
Lymphoid	*PTEN* mutations	150,151
	p85–EPH fusion (only one case reported)	75

EPH, ephrin; PI3K, phosphatidylinositol 3-kinase.

PHTS: Prevalenza

- A causa delle manifestazioni esterne variabili e spesso impercettibili di CS / BRRS, molti individui rimangono non diagnosticati

- Perciò, la vera prevalenza non è nota.
- La prevalenza di uno su 200.000 [Nelen et al 1999] è probabilmente una sottostima.

Diagnosi di Sindrome di Cowden

- La National Comprehensive Cancer Network [NCCN 2015] ha identificato un consenso sui seguenti criteri diagnostici clinici :

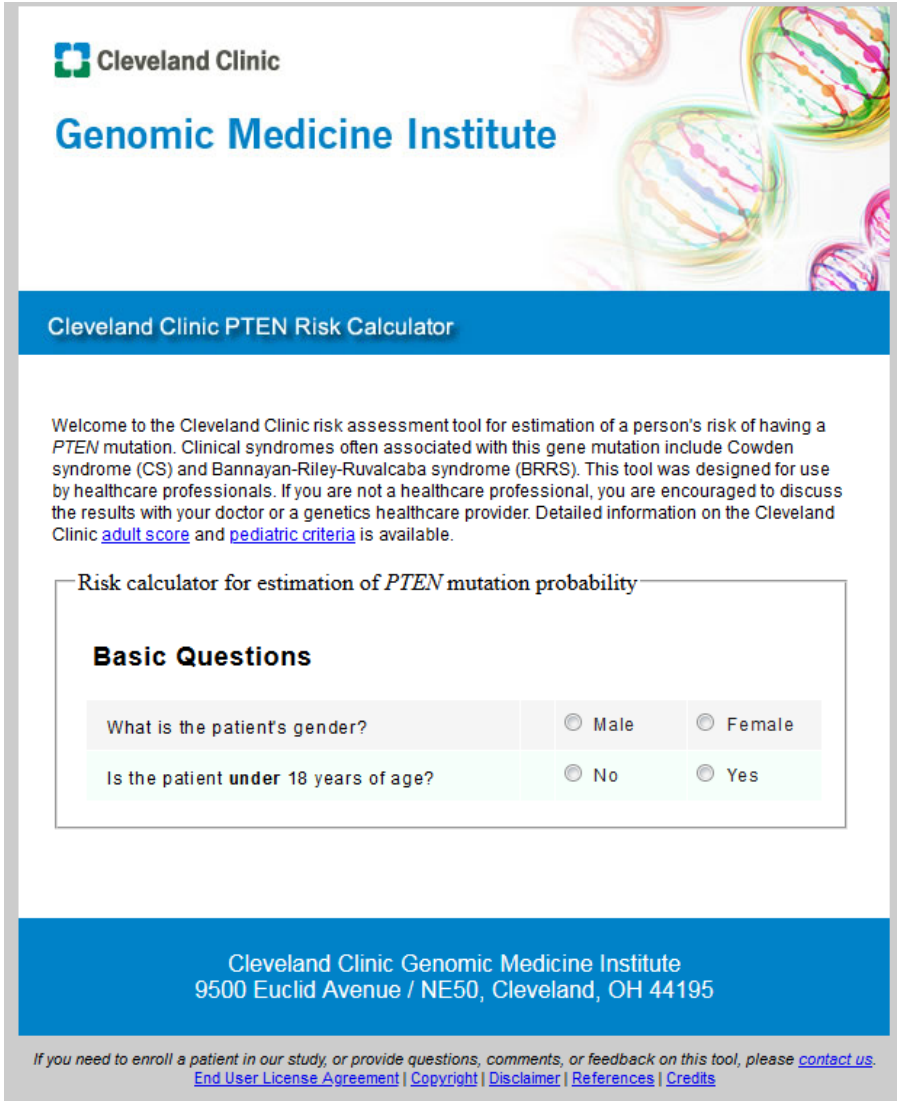
- ***Criteri patognomonici*** (criteri caratteristici di una particolare malattia): lesioni mucose e cutanee

- ***Criteri principali:*** carcinoma mammario, macrocefalia, carcinoma tiroideo e carcinoma endometriale

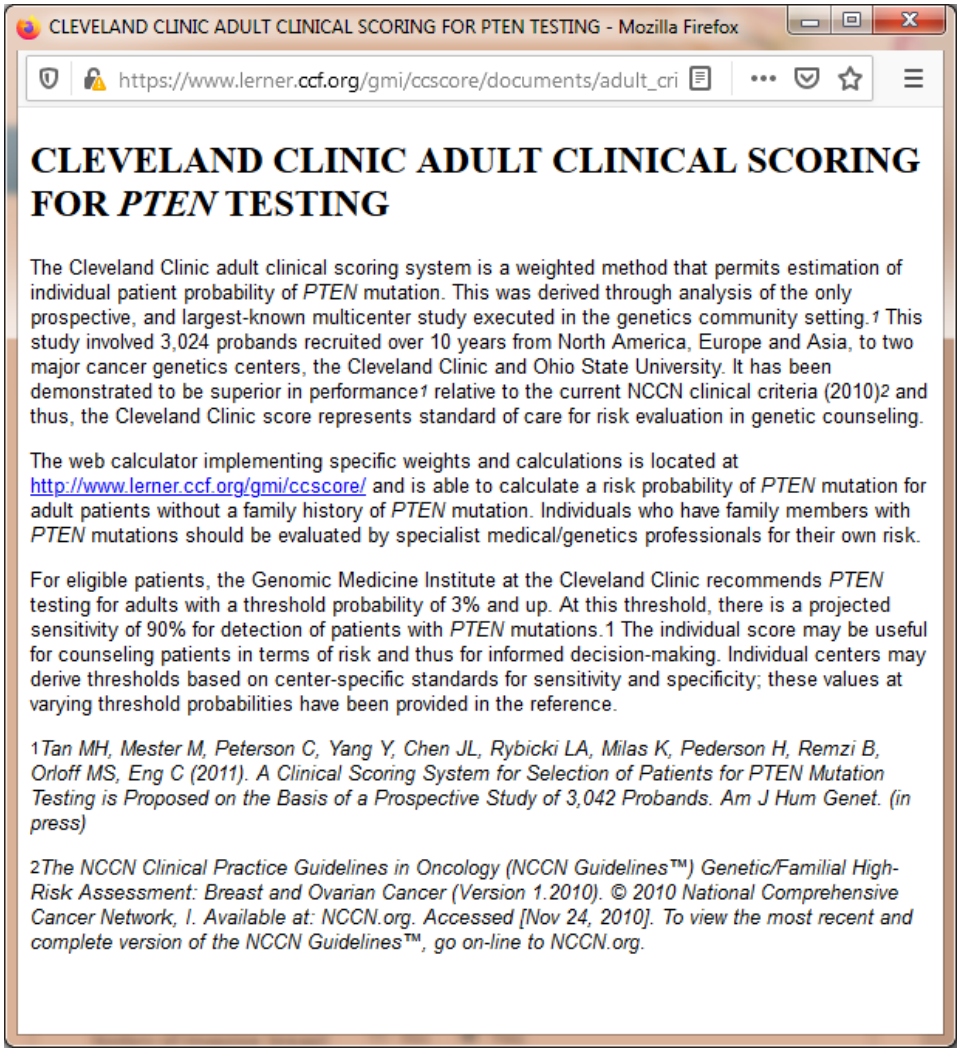
- ***Criteri minori:*** lesioni tiroidee, disabilità intellettiva, polipi intestinali amartomatosi, malattia fibrocistica del seno, lipomi, fibromi, tumori o malformazioni genitali e urinarie, fibromi uterini

Diagnosi: PTEN Cleveland Clinic Risk Calculator

- https://www.lerner.ccf.org/gmi/ccscore/



Diagnosi: PTEN Cleveland Clinic Risk Calculator



CLEVELAND CLINIC ADULT CLINICAL SCORING FOR PTEN TESTING - Mozilla Firefox

https://www.lerner.ccf.org/gmi/ccscore/documents/adult_cri

CLEVELAND CLINIC ADULT CLINICAL SCORING FOR *PTEN* TESTING

The Cleveland Clinic adult clinical scoring system is a weighted method that permits estimation of individual patient probability of *PTEN* mutation. This was derived through analysis of the only prospective, and largest-known multicenter study executed in the genetics community setting.[1] This study involved 3,024 probands recruited over 10 years from North America, Europe and Asia, to two major cancer genetics centers, the Cleveland Clinic and Ohio State University. It has been demonstrated to be superior in performance[1] relative to the current NCCN clinical criteria (2010)[2] and thus, the Cleveland Clinic score represents standard of care for risk evaluation in genetic counseling.

The web calculator implementing specific weights and calculations is located at http://www.lerner.ccf.org/gmi/ccscore/ and is able to calculate a risk probability of *PTEN* mutation for adult patients without a family history of *PTEN* mutation. Individuals who have family members with *PTEN* mutations should be evaluated by specialist medical/genetics professionals for their own risk.

For eligible patients, the Genomic Medicine Institute at the Cleveland Clinic recommends *PTEN* testing for adults with a threshold probability of 3% and up. At this threshold, there is a projected sensitivity of 90% for detection of patients with *PTEN* mutations.1 The individual score may be useful for counseling patients in terms of risk and thus for informed decision-making. Individual centers may derive thresholds based on center-specific standards for sensitivity and specificity; these values at varying threshold probabilities have been provided in the reference.

1Tan MH, Mester M, Peterson C, Yang Y, Chen JL, Rybicki LA, Milas K, Pederson H, Remzi B, Orloff MS, Eng C (2011). A Clinical Scoring System for Selection of Patients for PTEN Mutation Testing is Proposed on the Basis of a Prospective Study of 3,042 Probands. Am J Hum Genet. (in press)

2The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) Genetic/Familial High-Risk Assessment: Breast and Ovarian Cancer (Version 1.2010). © 2010 National Comprehensive Cancer Network, I. Available at: NCCN.org. Accessed [Nov 24, 2010]. To view the most recent and complete version of the NCCN Guidelines™, go on-line to NCCN.org.

Il test ha lo scopo di riconoscere possibili portatori di mutazioni germinali PTEN

Si basa su oltre 3000 probandi.

Nell'ambito della consulenza genetica, questo approccio appare superiore rispetto ai criteri NCCN (2010) per riconoscere pazienti con mutazioni germinali PTEN.

Diagnosi: PTEN Cleveland Clinic Risk Calculator

Adult Female

What is the patientâ€™s most recently measured head circumference?| video
Circumference: **19.6** inch | **50** cm

Is there a personal history of cancer?	No	Yes
Is there a personal history of developmental delay or autism?	No	Yes
Is there a personal history of thyroid disease?	No	Yes
Does the patient have any oral papillomas? | image 1 | image 2	No	Yes
Does the patient have any acral keratoses? | image 1	No	Yes
Does the patient have any skin lipomas?	No	Yes
Does the patient have a personal history of trichilemmomas, proven on biopsy? | image 1 | image 2	No	Yes
Are there any vascular malformations, located either superficially or internally?	No	Yes
Has the patient ever had a personal history of gastrointestinal polyps?	No	Yes
Has the patient ever had any uterine fibroids, also known as uterine leiomyomas?	No	Yes
Is there a history of glycogenic acanthosis found on upper gastrointestinal endoscopy?	No	Yes
Is there a personal history of a specific brain tumor called a dysplastic cerebellar gangliocytoma, also known as Lhermitte Duclos disease?	No	Yes
Is there a personal history of fibrocystic breast disease?	No	Yes

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Adult Male

What is the patient's most recently measured head circumference? | video
Circumference: **19.6** inch | **50** cm

Is there a personal history of cancer?	No	Yes
Is there a personal history of developmental delay or autism?	No	Yes
Is there a personal history of thyroid disease?	No	Yes
Does the patient have any oral papillomas? | image 1 | image 2	No	Yes
Does the patient have any acral keratoses? | image 1	No	Yes
Does the patient have any skin lipomas?	No	Yes
Does the patient have freckling of the penis?	No	Yes
Does the patient have a personal history of trichilemmomas, proven on biopsy? | image 1 | image 2	No	Yes
Are there any vascular malformations, located either superficially or internally?	No	Yes
Has the patient ever had a personal history of gastrointestinal polyps?	No	Yes
Is there a personal history of glycogenic acanthosis found on upper gastrointestinal endoscopy?	No	Yes
Is there a personal history of a specific brain tumor called a dysplastic cerebellar gangliocytoma, also known as Lhermitte Duclos disease?	No	Yes

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Diagnosi: PTEN Cleveland Clinic Risk Calculator

Pediatric

What is the patientâ€™s most recently measured head circumference? | video

Circumference: **18.5** inch | **50** cm

What was the age of the patient when the head circumference was measured? (round to nearest whole year).	**Age:** **9** year(s)	
Has the patient ever been diagnosed with autism, developmental delay, or mental retardation?	No	Yes
Are there suggestive skin lesions such as lipomas, biopsy-proven trichilemmomas [image], or skin hemangiomas?	No	Yes
Are there mucosal features such as oral papillomas or freckling on the penis ?	No	Yes
Does the patient have either superficial or internal arteriovenous malformations?	No	Yes
Has the patient ever been diagnosed with gastrointestinal polyps?	No	Yes
Does the patient have a personal history of thyroid cancer?	No	Yes
Is there a personal history of germ cell tumors, including testicular or ovarian cancers/tumors?	No	Yes

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CLEVELAND CLINIC ADULT CLINICAL SCORING FOR PTEN TESTING - Mozilla Firefox

https://www.lerner.ccf.org/gmi/ccscore/documents/pediatric

CLEVELAND CLINIC PEDIATRIC CLINICAL CRITERIA FOR *PTEN* TESTING

The Cleveland Clinic pediatric clinical criteria is a systematic criteria based on evaluation of a large series of pediatric individuals with *PTEN* mutations.[1] These include patients who have been diagnosed with Cowden syndrome or Bannayan-Riley-Ruvalcaba Syndrome (BRRS). The criteria is applicable to patients without a family history of *PTEN* mutations. Individuals who have family members affected with *PTEN* mutations should be evaluated by specialist medical/genetics professionals.

CRITERIA

1. Macrocephaly (≥ 2 standard deviations from normal)
2. At least one of the following four additional criteria should be present:
   a. Autism or developmental delay
   b. Dermatologic features, including lipomas, trichilemmomas, oral papillomas, or penile freckling
   c. Vascular features, such as arteriovenous malformations, or hemangiomas
   d. Gastrointestinal polyps

Other clinical diagnoses that should lead to evaluation for the above clinical features include pediatric onset thyroid cancer and pediatric onset germ cell tumors.

The Cleveland Clinic criteria for adult and pediatric subjects has been demonstrated to be superior in performance to the current NCCN clinical criteria (2010) in selection of patients for *PTEN* mutation screening. This evaluation was reported in the only prospective study conducted in 3,024 probands recruited over 10 years.[1]

1 Tan MH, Mester M, Peterson C, Yang Y, Chen JL, Rybicki LA, Milas K, Pederson H, Remzi B, Orloff MS, Eng C (2011). A Clinical Scoring System for Selection of Patients for PTEN Mutation Testing is Proposed on the Basis of a Prospective Study of 3,042 Probands. Am J Hum Genet. (in press)

Diagnosi: PTEN Cleveland Clinic Risk Calculator

Cleveland Clinic

PTEN Cleveland Clinic Score Calculator

Report for _____

Based on the information provided, the estimated probability of a PTEN gene mutation for the adult subject is 91%. PTEN gene testing is recommended for patients with an estimated probability of 3% and up.

Due to statistical variation, the precise estimate varies between 73.5% and 97.3 % .

This estimate is based on a total risk score of 32 .

Indicazione per svolgere analisi per mutazioni geniche PTEN

- Breast cancer at age 41
- Thyroid goiter or Thyroid nodules or Thyroid adenomas or Hashimoto's thyroiditis
- Oral papillomas
- Acral keratoses
- Skin lipomas
- Trichilemmomas
- Vascular malformations
- Uterine fibroids
- Fibrocystic breast disease

This tool was designed for use by health professionals. This result should be interpreted together with additional information including, and not limited to, a physical examination and detailed family history taken by a skilled medical/genetics professional.

For more information or to enrol in our study, please contact the Genomic Medicine Institute at: Genomic Medicine Institute, Cleveland Clinic Mailstop NE-50 9500 Euclid Avenue, Cleveland, Ohio 44195; Email: pten@ccf.org Tel: (216) 445-7862. Fax: (216) 636-0009

Analisi di Genetica molecolare

- La diagnosi di PHTS viene stabilita in un probando mediante l'identificazione di una variante patogena PTEN germinale eterozigote su test genetici molecolari.

- In caso di assenza di mutazioni PTEN, in soggetti con sindrome di Cowden (CS) e sindrome simile a Cowden sono da considerare anche l'analisi della metilazione del promotore del gene killin (KLLN), e l'analisi mutazionale del gene SDHB-D, codificante per una subunità della succinato deidrogenasi

Gestione dei pazienti dopo la diagnosi iniziale

- Poiché la sindrome di Cowden è associata ad un aumentato rischio per alcuni tipi di cancro, la gestione è generalmente mirata alla diagnosi precoce

- Quando una variante patogena PTEN viene identificata in un probando, i test genetici molecolari su parenti asintomatici a rischio possono identificare coloro che hanno la variante patogena specifica della famiglia e garantire la sorveglianza medica.

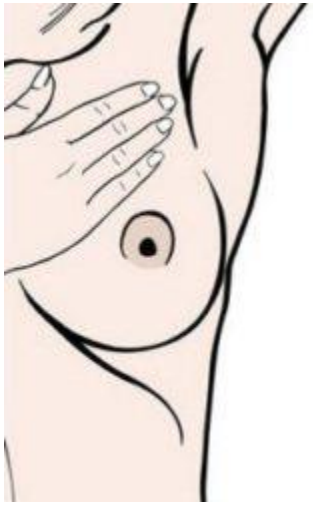
- *Sorveglianza*: rilevare tumori nelle prime fasi, più facilmente curabili

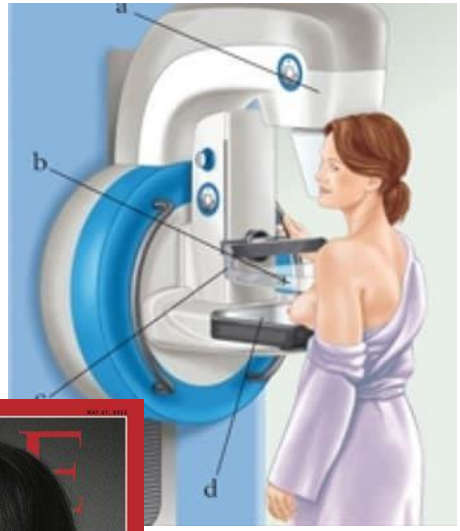
Gestione dei pazienti dopo la diagnosi iniziale

Per donne

- Autoesame del seno a partire da 18 anni
- Esami clinici del seno ogni 6-12 mesi a partire dall'età di 25 anni (o individualizzati in base alla prima diagnosi di cancro in famiglia)
- Mammografia annuale e risonanza magnetica mammaria a partire dai 30-35 anni (o individualizzata sulla base della prima diagnosi di cancro in famiglia)
- Lo screening annuale per carcinoma endometriale con ultrasuoni e / o biopsia casuale può essere preso in considerazione a partire dai 30-35 anni

- Gli interventi di profilassi chirurgica possono essere considerati un'opzione preventiva per alcune forme di cancro

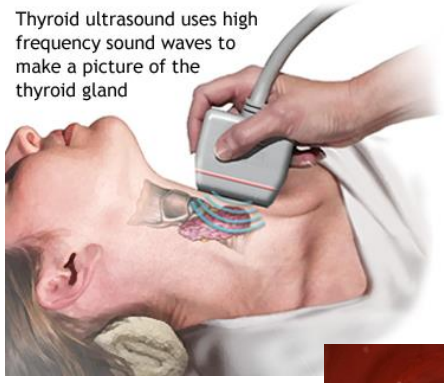


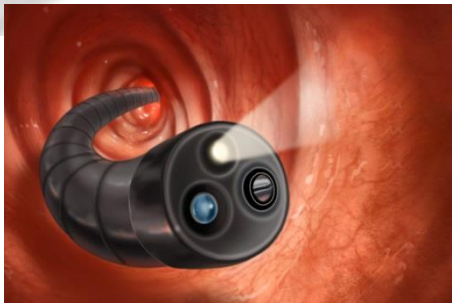


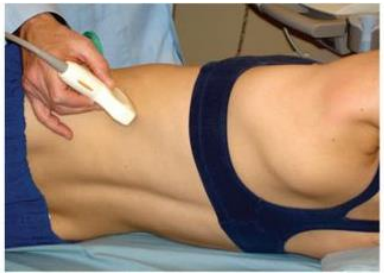
Management of patients after initial diagnosis

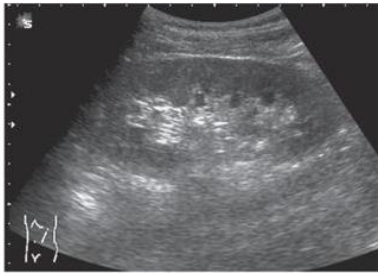
Per adulti (Uomini e donne)

- Esame fisico annuale a partire dall'età di 18 anni
- Ecografia tiroidea annuali a partire dall'età di 18 anni
- Colonscopia basale all'età di 35 anni con follow-up ogni 5 anni (più frequente se identificati polipi)
- Ecografia renale ogni 1-2 anni a partire dai 40 anni





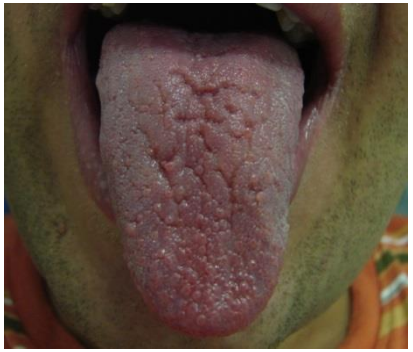




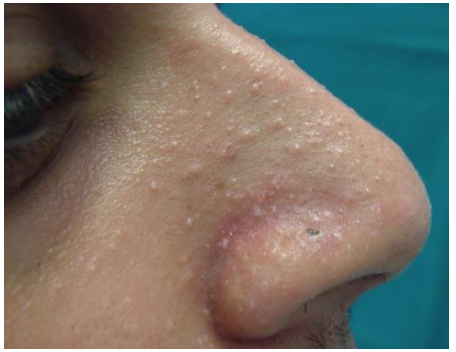
Management of patients after initial diagnosis

Pediatrico

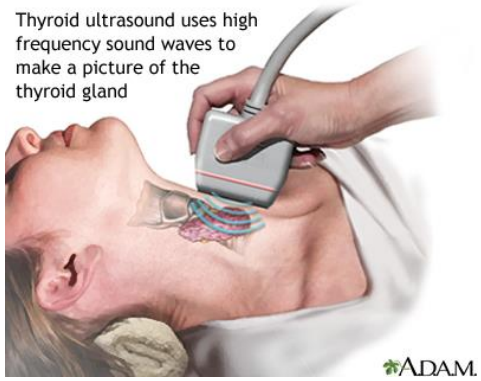
- Controllo annuale della pelle con esame fisico
- Esame ecografico annuale della tiroide (a partire dall'identificazione di una variante patogena PTEN)
- Valutazione dello sviluppo cranico



papillomatous papules



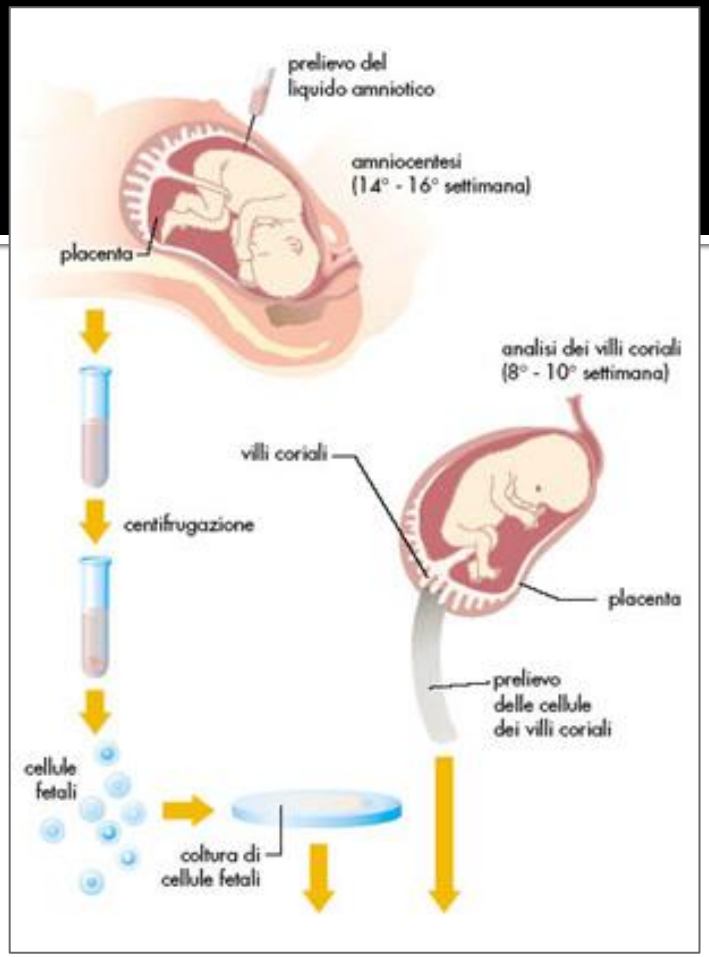
Small papules

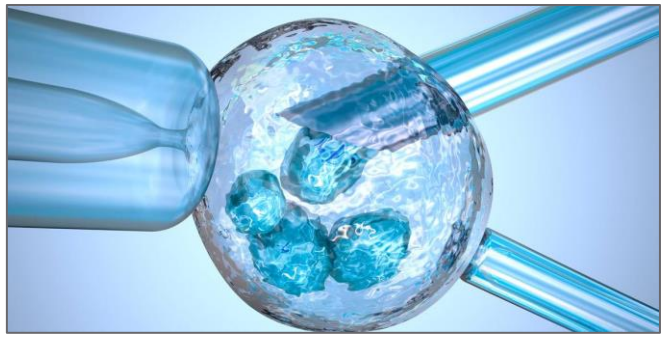


Analisi prenatale e preimpianto

- Una volta identificata la variante patogena PTEN nella famiglia,

- Sono possibili
  - test prenatali per una gravidanza ad aumentato rischio
  - diagnosi genetica preimpianto per PHTS





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