fate
associazione Famiglie con ATresia Esofagea

I° Incontro Nazionale
Associazione Famiglie con Atresia Esofagea
26-27 Settembre 2015

L'abc dell'atresia esofagea e delle patologie associate, rispondiamo insieme alle domande fondamentali

TRASMISSIBILITÀ EREDITARIA, CAUSE GENETICHE, SINDROMI E MALFORMAZIONI ASSOCIATE

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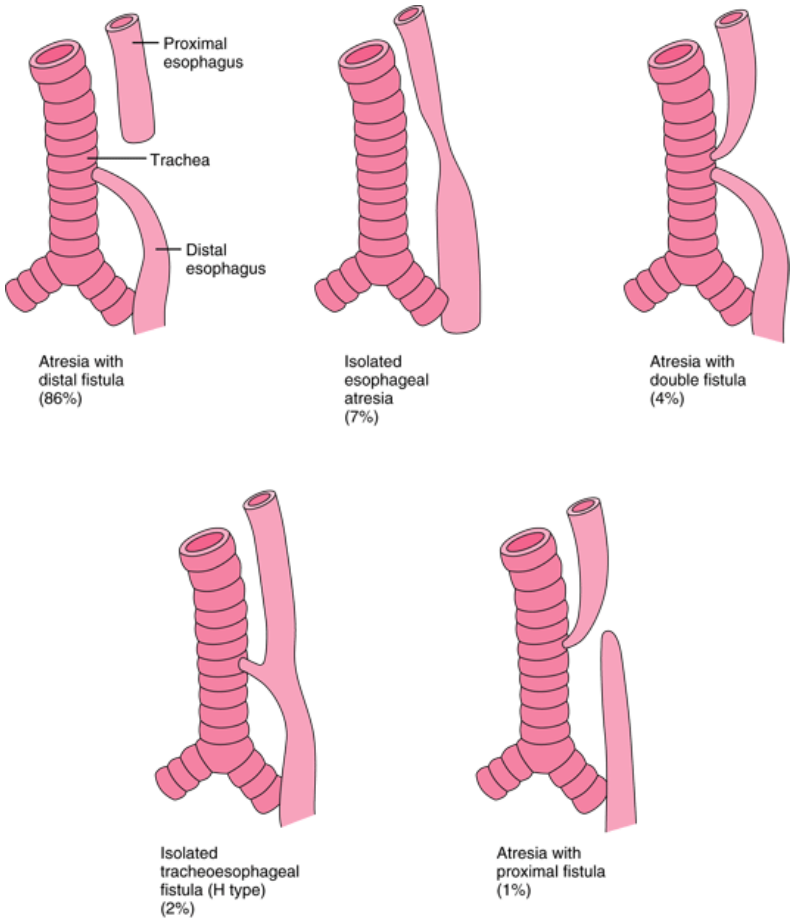
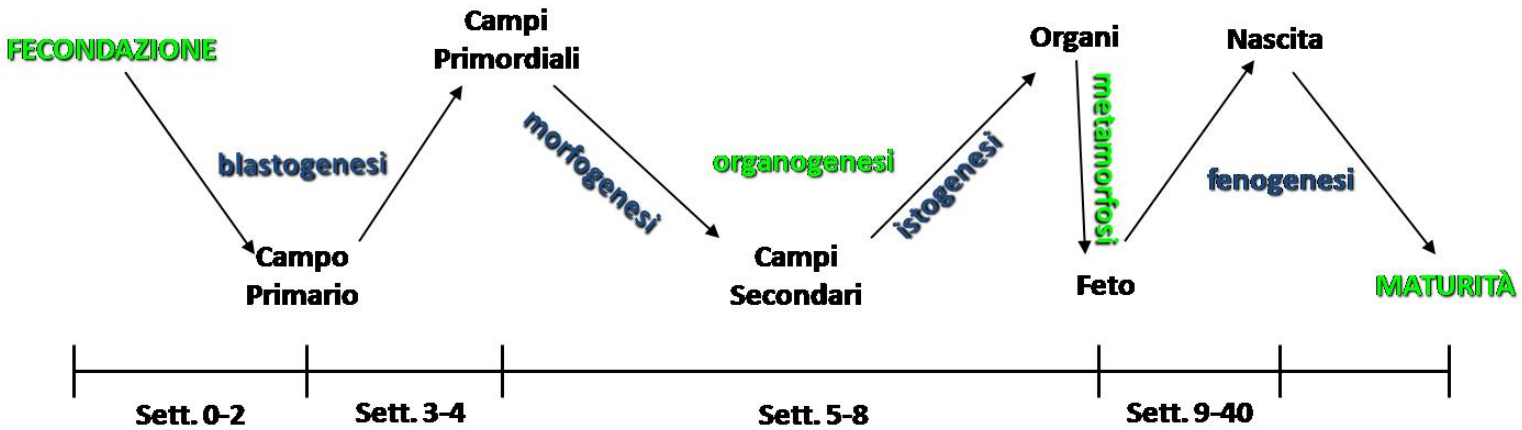
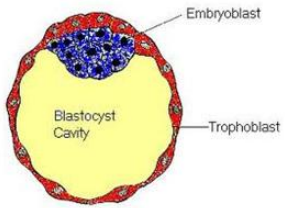
FREQUENZA E CLASSIFICAZIONE

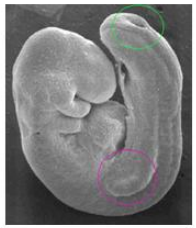
Frequenza alla nascita: ~1/3.500



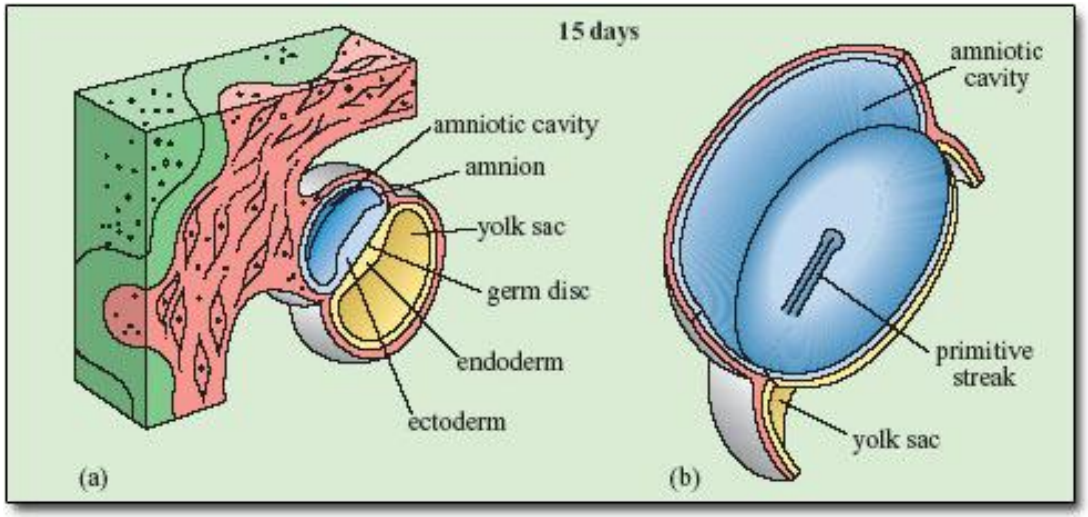
TIMING

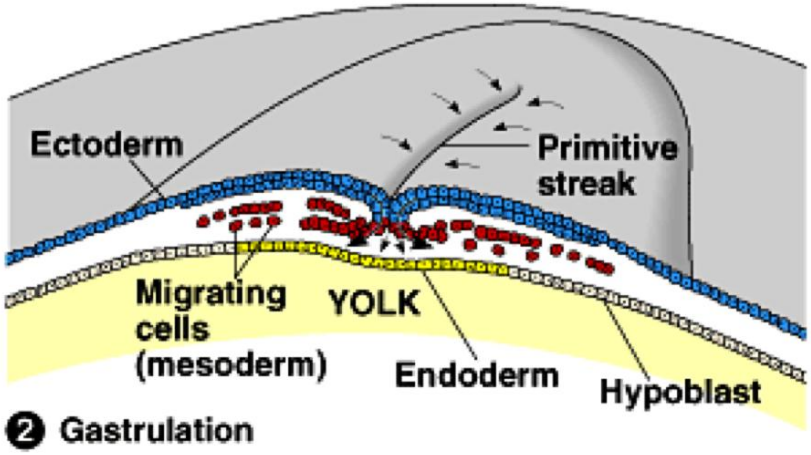

FECONDAZIONE
blastogenesi
Campo Primario
Campi Primordiali
morfogenesi
organogenesi
Campi Secondari
istogenesi
Organi
metamorfosi
Feto
Nascita
fenogenesi
MATURITÀ
Sett. 0-2
Sett. 3-4
Sett. 5-8
Sett. 9-40


Embryoblast
Blastocyst Cavity
Trophoblast

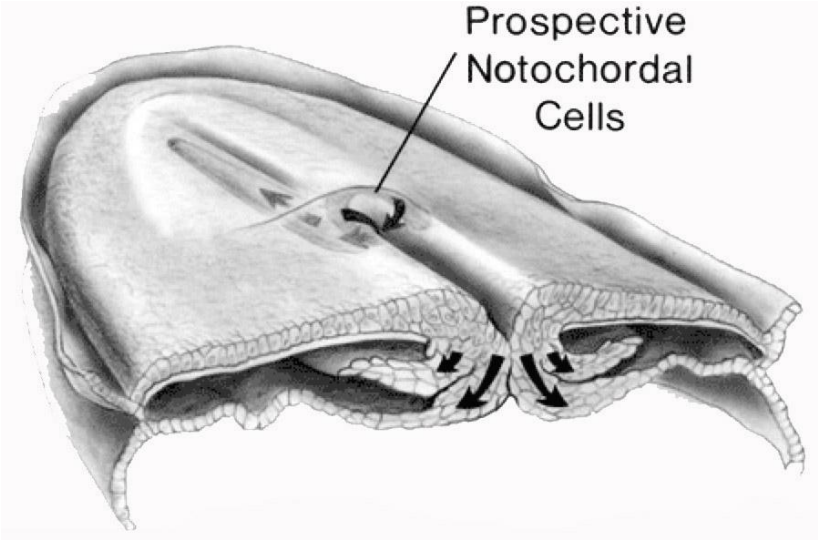


TIMING: 3° SETTIMANA

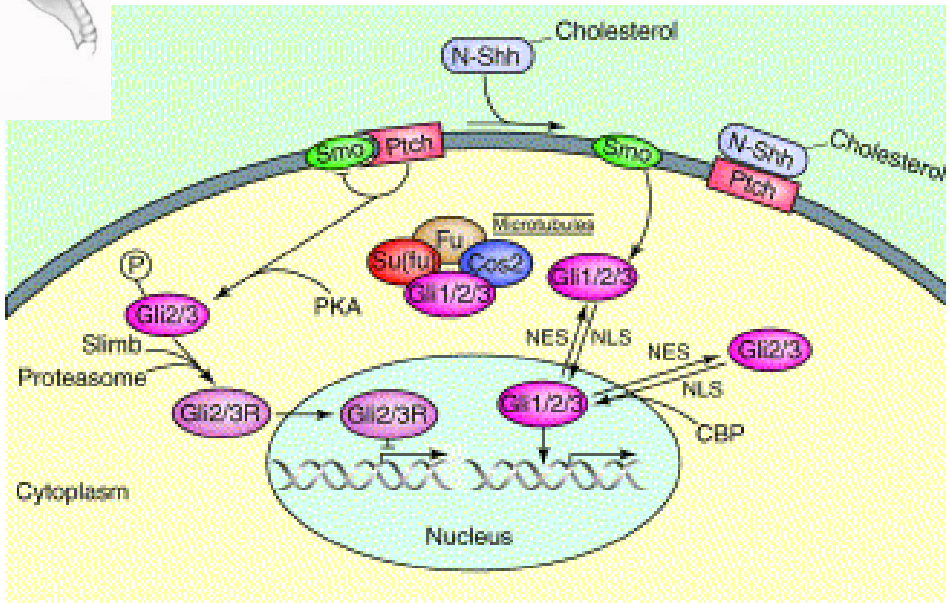




TIMING: SHH PATHWAY



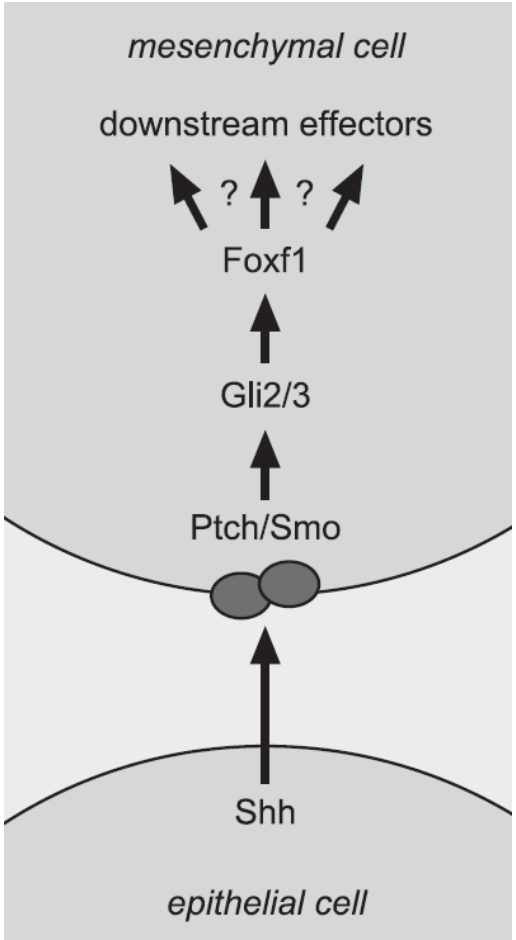
Linea primitiva
come “campo dello
sviluppo”



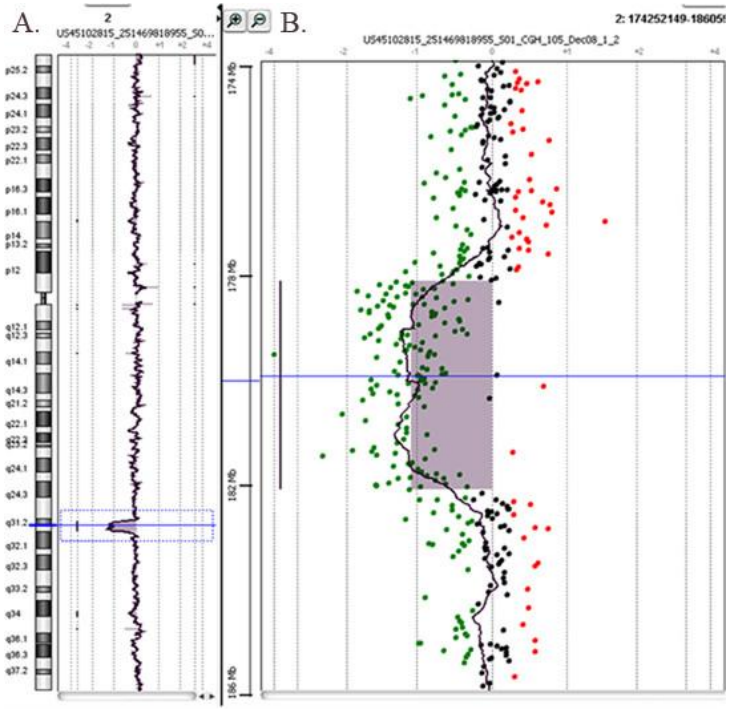
TIMING: SHH PATHWAY

Mouse gene	Lung/foregut phenotype	Phenotype (other)	Reference	Human gene	Locus	Mutations	Lung/ foregut phenotype	Phenotype (other)
Shh	Esophageal atresia, tracheo-esophageal fistula, lung anomalies	Abnormalities of CNS; cyclopia; distal limb truncation; abnormalities of axial skeleton, renal agenesis, abnormalities of heart looping, intestinal malrotation, annular pancreas, duodenal stenosis, intestinal transformation of the stomach, abnormal gut innervation, imperforate anus	[9,29,46]	*SHH*	7q36	YES	NR	Holoprosencephaly [HPE3, OMIM 142945], microphthalmia [OMIM 611638]
Foxf1	Esophageal atresia, tracheo-esophageal fistula, lung lobe fusion defects, pulmonary vascular defects	Axial skeletal defects	[22,35]	*FOXF1*	16q24.1	YES	Alveolar capillary dysplasia	Intestinal malrotation, atrio-ventricular canal defect, renal malformations
Gli2	*Gli2*−/− mice are normal. Gli2 −/− Gli3+/− mice have esophageal atresia tracheo-esophageal fistula. *Gli2*−/− *Gli3* −/− mice have absent oesophagus, trachea and lungs	NR	[39]	*GLI2*	2q14	YES	NR	Holoprosencephaly
Gli3	See *Gli2* entry	*Gli3*−/− mice are allelic with Xt. They have synpolydactyly and brain malformations.	[39]	*GLI3*	7p13	YES	NR	Greig cephalopolysyndactyly syndrome [GCPS, OMIM 175700]; Pallister–Hall syndrome [PHS, OMIM 146510] (imperforate anus, polydactyly, hypopituitarism, hypothalamic hamartoblastoma)
Noggin	Esophageal atresia, tracheo-esophageal fistula	Failure of closure of neural tube, exencephaly, wide, club-shaped limbs, shortened, abnormal body axis, lethality at birth	[27,43]	*NOGGIN*	17q22	YES	NR	Proximal symphalangism with multiple synostoses; stapes ankylosis with broad thumbs and toes; brachydactyly type B2
Sox2	Esophageal atresia, tracheo-esophageal fistula	Neurodegeneration, impaired neurogenesis	[13,44]	*SOX2*	3q26.3	YES	Esophageal atresia	Anophthalmia, genitourinary malformations

SHH, FOXF1 E VACTERL



Alcuni pazienti con associazione VACTERL presentano delezioni multigeniche incluso FOXF1



VACTERL ED ETEROGENEITA'

V= vertebral (difetti vertebrali)
A= anal(atresia anale)
C= cardiac (difetti cardiaci)
TE= tracheo-esophageal (atresia esofagea +/- fistola)
R= renal and radial (anomalie renali e radiali)
L= limb (altri difetti agli arti)

Diagnosi "di esclusione"

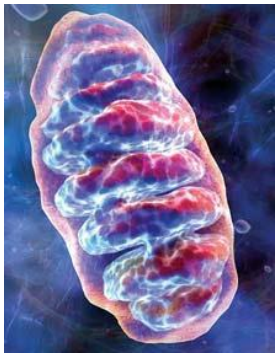
Presenza di un "numero" di difetti in assenza di sindromi note

Tendenza prevalente: almeno 3 difetti preferibilmente in tre segmenti corporei differenti (arti, torace, addome)

Frequenza: ~1/12.500

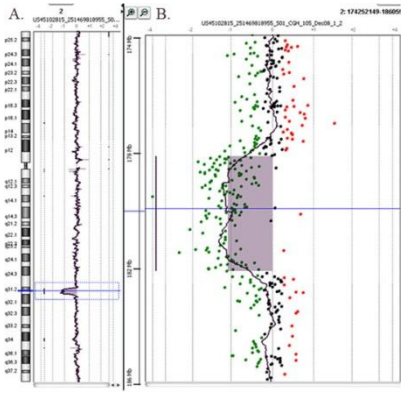
VACTERL ED ETEROGENEITA'

Mutazioni mitocondriali



Eventi stocastici

Microdelezioni/duplicazioni



VACTERL

Mutazioni DNA

Diabete materno

VACTERL ED ETEROGENEITA'

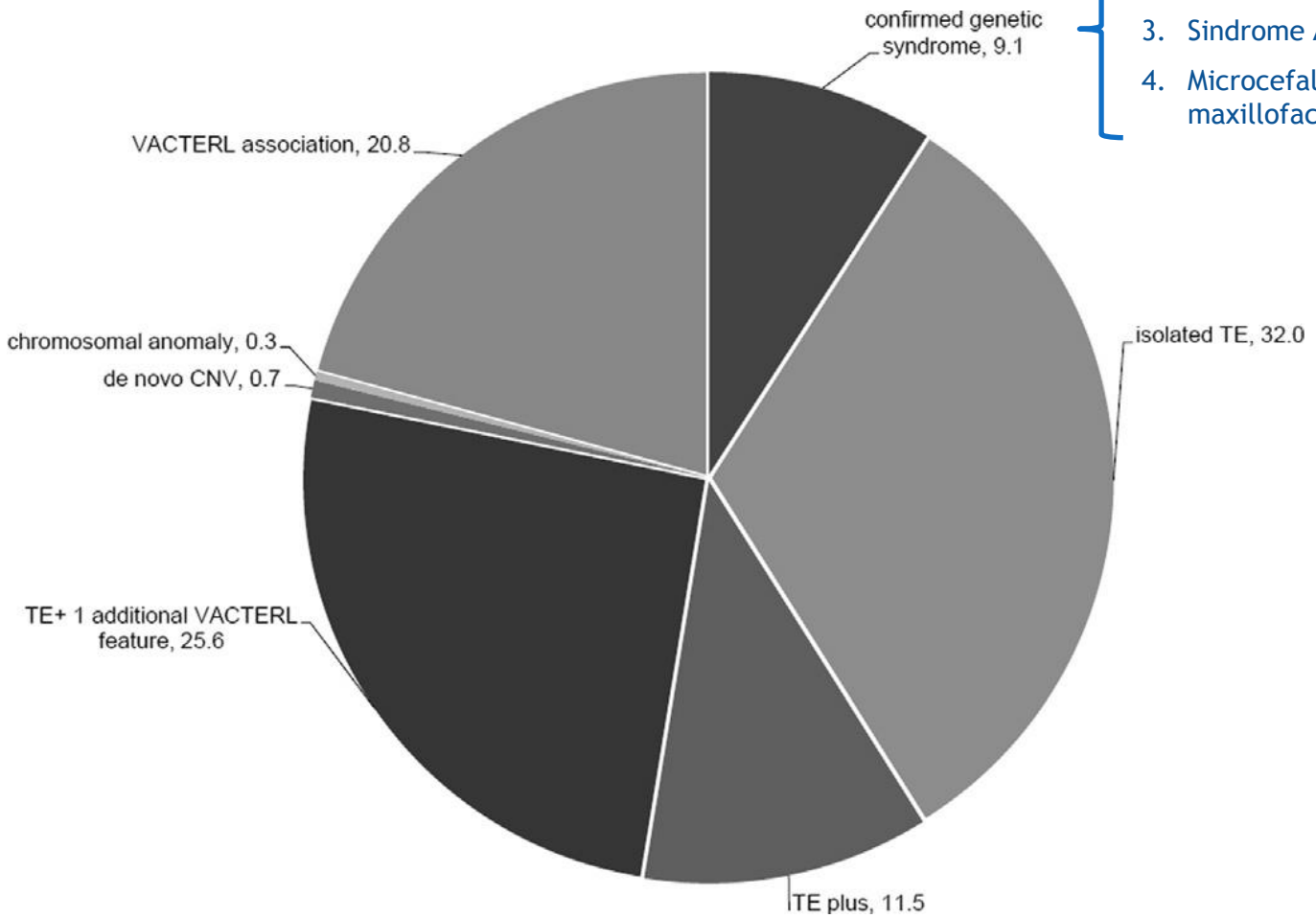
Checklist "genetico":

1. Storia familiare
2. Storia della gravidanza (teratogeni, gemellarità, ecc)
3. Cariotipo standard
4. *CGH array
5. **analisi mutazionale di singoli geni (*ZIC3*, *FOXF1*, *FGF8*, *PCSK5*, ecc)
6. **analisi DNA mitocondriale

(solitamente)
Rischio di ricorrenza basso (<3%, 3-5%)
Monitoraggio ecografico

ATRESIA ESOFAGEA ED ETEROGENEITA'

1. Sindrome di Feingold
2. Sindrome CHARGE
3. Sindrome AEG
4. Microcefalia-disostosi maxillofacciale



COSA ASPETTARSI DALLA GENETICA MEDICA

1. Diagnosi differenziale (isolata vs associata)
2. Inquadramento nosologico
3. Orientamento assistenziale
4. Presa in carico a lungo termine (specifici aspetti)
5. Stima dei rischi di ricorrenza
6. Opzioni riproduttive
7. Pianificazione future gravidanze

COSA ASPETTARSI DALLA GENETICA MEDICA

GRAZIE MILLE PER L'ATTENZIONE!!!