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Pediatric Drug Development - Visionary Promise or Nightmare?

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Melanoma: Two Good News, And A Bad One

- Metastatic conventional malignant melanoma (CMM) ***was*** untreatable and lethal; combinations (dabrafenib + trametinib,vemurafenib + cobimetinib, nivolumab + ipilimumab) allow effective treatment today.
- Most “pediatric“ melanomas are CMM in adolescents, and there are pediatric melanomas: Spitz nevus, Spitzoid melanoma, melanoma from giant congenital nevi. Genomic differentiation is possible.
- The bad news: underage CMM patients are wrongly treated by FDA- or EMA-triggerd monotherapy studies: medically senseless, and they prevent better combination treatment
- **Why?**

The Therapeutic Orphans Concept

- Since 1950ies drug toxicities reported in newborns (AAP1995)
- Since 1962: pediatric warnings appeared in drug labels.
- Shirkey claimed these denied children use of modern drugs and characterized children as "therapeutic orphans"
- AAP* claims:

- Drug treatment of children is experimental unless FDA-certified - Children of all ages fundamentally different from adults - *“moral imperative to formally study drugs in children“*

- US law rewards pediatric studies since 1997
- **What are children?**

Definitions of Children

- Stone age: capacy to kill in combat (♂)/ get pregnant (♀)
- Later: adulthood ceremonies
- Secular societies: age
- Age limits are different for various aspects: alcohol, driving, firearms, criminal law
- For pharmaceutical treatment *should* be science-based, but is based on ***administrative*** age limits: US <16, EU <18 years
- For pharmaceutical treatment, we need physiological definition of children/ adolescents

PIPs* & WRs** In A Nutshell

- Many FDA WRs, almost all PIPs demand separate pharmacokinetic (PK) studies and proof of efficacy in minors of all age groups.
- Dose-finding and PK studies in adolescents are scientifically worthless. These patients have already an adult body
- Dose-finding in children is reasonable, proof of efficacy is not
- Newborns mature. From ~1 year of age, roughly, their absorption, distribution, metabolism, excretion (ADME) is comparable to adults
- ***One*** human species – homo sapiens sapiens, or ***two*** **?** adultus vs. praetextatus [infantilis/ pupillus/ adolescens].

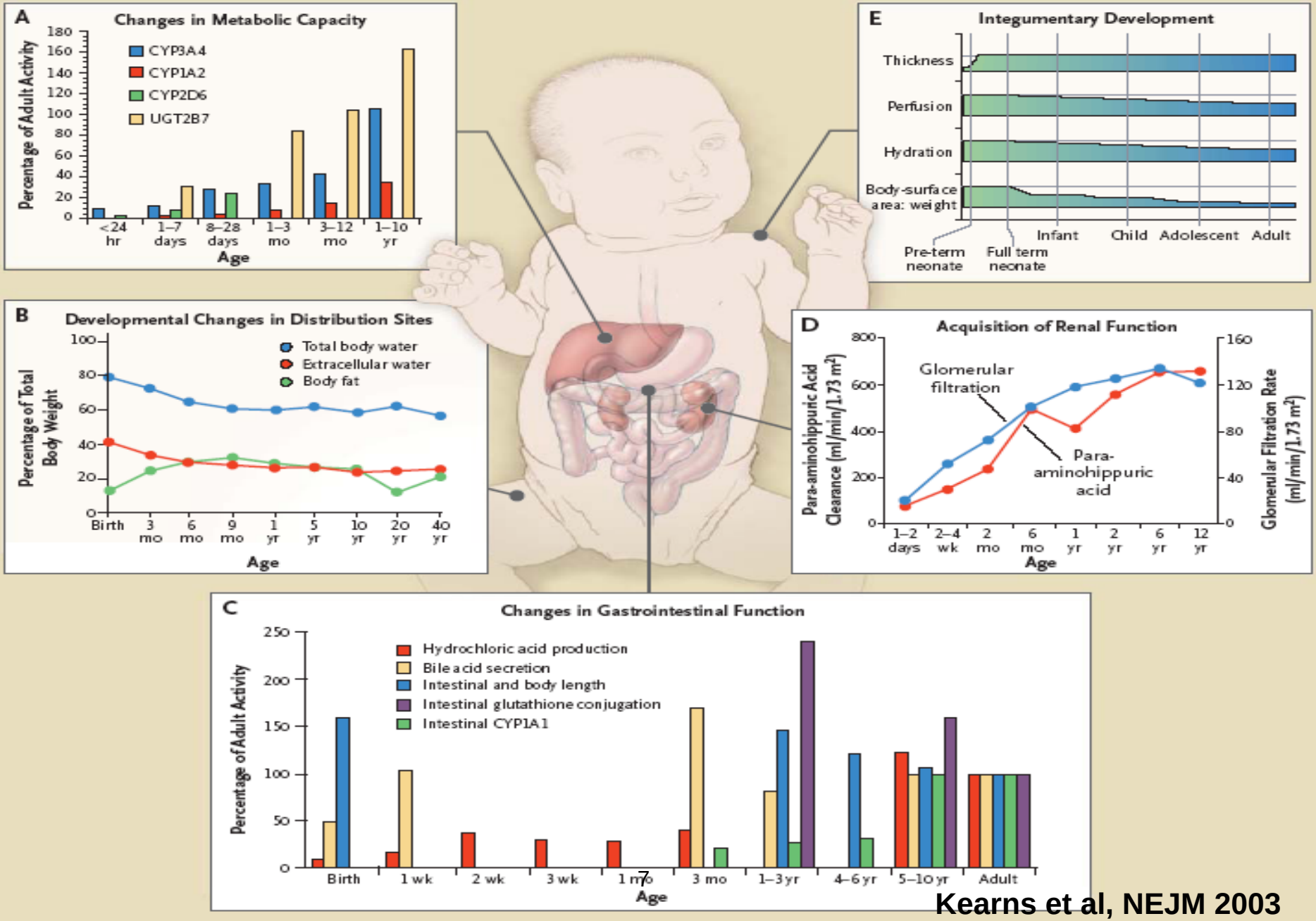
***PIP**: EU pediatric investigation plan

****WR**: FDA written request

Melanoma, EMA, FDA

- Twelve melanoma PIPs, one FDA melanoma written request (WR)
- Two industry-sponsored melanoma studies in adolescents had to be terminated in 2016. Ipilimumab: triggered by both FDA WR & EMA PIP, vemurafenib: PIP-triggered only
- The therapeutic orphan concept originated in the US. Massively expanded by the EU regulation, with now >1000 PIPs

Kearns et al. 2003: ADME in Children



Kearns et al, NEJM 2003

Potentially Largest Worldwide Abuse of Patients in Research in History

- EU defines as children everybody under 18 years
- Most studies demanded by > 1000 PIP are medically senseless
- Many harm by preventing efficient treatment or participation in better trials, including melanoma, leukemia allergic rhinitis, psoriasis
- PIPs demand ***regulaty S&E* studies*** as if <18 were another species
- Performed by unsuspending clinicians, unaware of PIP background
- Approved by unsuspecting Institutional IRBs/ECs
- Mechanisms established in response to world war II crimes, to Beecher 1966, & to Tuskegee trial have failed.
- Varies for patients between “only“medically senseless study participation up to preventing effective treatment in a lethal

Conflicts of Interest, Switzerland, The Way Forward

- An industry of “pediatric“ studies has developed in clinical academia
- Largest clinical groups that benefit from pediatric research: pediatric oncology & rheumatology (JIA*) with obvious conflict of interest
- Strong conflicts of interest also for FDA/EMA: stronger standing in the triangle of clinical care, drug development and regulatory authorities
- New definition of conflicts of interest needed by international medical publishing & COPE (Committee on Publication Ethics)
- Public debate will rock the trust in authorities and academic researach, but will be unavoidable
- Switzerland as an independent country has the chance to set a legal precedent for physiology-based pharmaceutical law

*JIA: juvenile idiopathic arthritis

Current Developments

FDA

- Accepts extrapolation of efficacy for antiepileptic drugs (partial onset seizsures) down to 4 years; for anticancer avelumab down to 12 y
- Topical dermatology compound approved with study in 2-79 years
- No critical review of collaboration with the EMA … yet
- In its 2016 report to congress also expressed EMA-like wishes e.g. in ped oncology

AAP*

- From 1977 on, contradictory positions: focus on methodology and labels, but also pragmatic positions towards off-label use
- Should revise position towards therapeutic orphans

EMA: Class waivers list modified in 2015: more PIPs in rare diseases, including liver cancer and Parkinson's disease

EAP**: No position. EU Commission's assessment in newest

***AAP** American Academy of Pediatrics ****EAP** European Academy of Pediatrics

Conclusions

- Pediatric legislation: blur @ interface of medicine and law
- Children did fully participate at pharmaceutical progress
- Pediatric legislation resulted in – unexpected - abuse of patients
- Is ***societal*** challenge. Media, physicians, lawyers, advocacy groups will address this. Pediatricians shouldn't stand aside
- Will rock public trust in health system & regulatory authorities
- Will help to improve research & drug development
- Will allow industry to re-calibrate its societal perception
- Might lead to interesting alliances, e.g. big pharma & DNDi*
- US & EU pediatric legislation need thorough

***DNDi** **D**rugs for **N**eglected **D**iseases **i**nitiative

Outlook

- Science: high-level journals
- Scientific organisations: AAP, EAP, disease-specific organisations
- Industry representations
- Patient representatives
- Groups that represent Swiss science
- ?Conferences in Switzerland, EU, elsewhere?

Thank You For Your Attention!

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Back-Ups

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Conflicts of Interest (CoIs)

- Traditional CoI: payment by industry
- The “therapeutic orphans” concept strengthened the role of regulatory authorities, led to funding of ped research.
- Institutions, clinicians, clinical research organisations’ (CROs’) CoIs: positive public image, funds, publications, networking
- Pediatric legislation created ***market*** for pediatric clinical trials
- But most authority-demanded studies are medically senseless

The “Therapeutic Orphans Concept”: A Dogma

- Shirkey & AAP used “children“ as ***legal*** and ***physiological*** term
- Resulted in inadequate physiological connotation to a legal term
- AAP & FDA regarded pediatric labels as way forward
- “Therapeutic Orphans“: catchy blur @ interface of law & medicine
- Kids need ***dosing*** information, not separate proof of safety & efficacy
- Already FDAMA & PREA were based on flawed concept

EMA Melanoma PIPs	
Compound	**PIP number**
Binimetinib	EMEA-001454-PIP03-15
Cobimetinib	EMEA-001425-PIP01-13-M01
Dabrafenib	EMEA–001147-PIP01-11-M03
Encorafenib	EMEA-001588-PIP01-13
Ipilimumab*	EMEA-000117-PIP02-10* • EMEA-000117-PIP02-10-M07
MAGE-A3 recombinant protein**	EMEA-001099-PIP02-11** • EMEA-001099-PIP02-11-M01
Nivolumab	EMEA-001407-PIP01-12
Paclitaxel	EMEA-001308-PIP01-12
Pembrolizumab	EMEA-001474-PIP01-13
Selumetinib	EMEA-001585-PIP01-13
Trametinib	EMEA-001177-PIP01-11-M02
Vemurafenib**	EMEA-000978-PIP01-10** • EMEA-000978-PIP01-10-M01
* First ipilimumab melanoma PIP @ EMA document library.	
**PIPs later changed into waivers	

First Two Ipilimumab WR-requested Clinical Studies

1. An open label, dose-escalation study of ipilimumab in pediatric patients (aged 1 to 21 years) with refractory cancers.
2. A clinical study of ipilimumab in pediatric patients (12 to < 18 years) with unresectable or metastatic melanoma to evaluate PK and safety.
    - Efficacy in adolescent patients (12 to < 18 years) will be determined by extrapolation from results observed in adult patients treated with ipilimumab for unresectable or metastatic melanoma.

EMA EUPL 10-Years Report – Page 14

- **Rheumatology**: 14 PIPs completed, → approval of 8 new paediatric indications. New treatments authorised for JIA* including canakinumab, abatacept, etanercept, adalimumab
- **Cardiovascular diseases**: New treatments authorized following PIPs, including valsartan & losartan for hypertension; rosuvastatin, atorvastatin, ezetimibe for hypercholesterolaemia.
- **Infectious diseases**: Available after PIP completion, incl.: peginterferon α, ribaravin, entecavir for hepatitis C; atazanavir, darunavir, lopinavir/ritonavir, lamivudine/raltegravir & nevirapine for HIV; voriconazole & caspofungin for fungal infections; new antibiotics.
- **Pediatric oncology**: Newly available for children: recombinant asparaginase for ALL*, dinutuximab for neuroblastoma

***JIA** Juvenile idiopathic Arthritis
***ALL** Acute Lymphatic Leukemia

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