# Medical Treatment of Cushing's Syndrome

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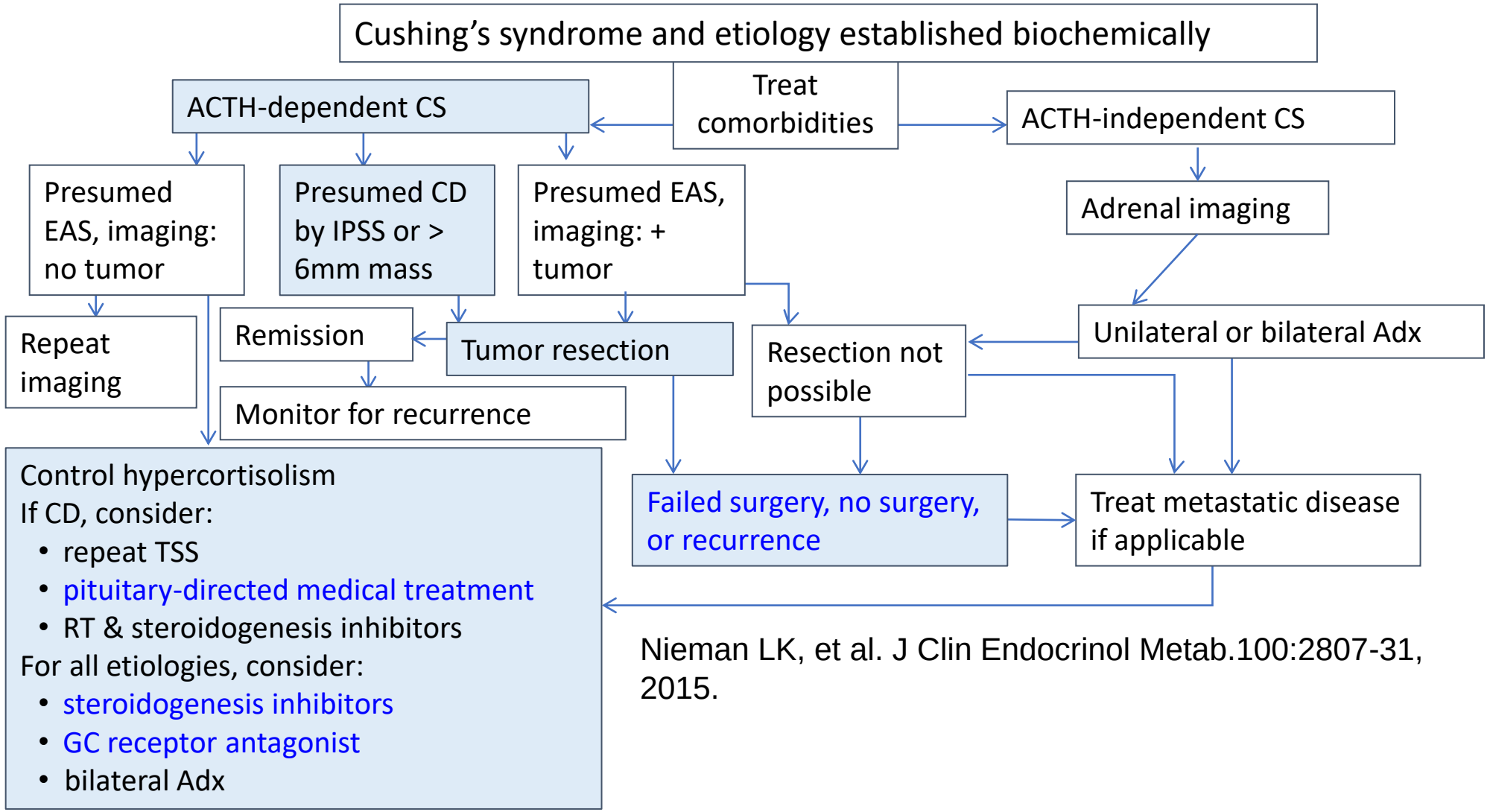
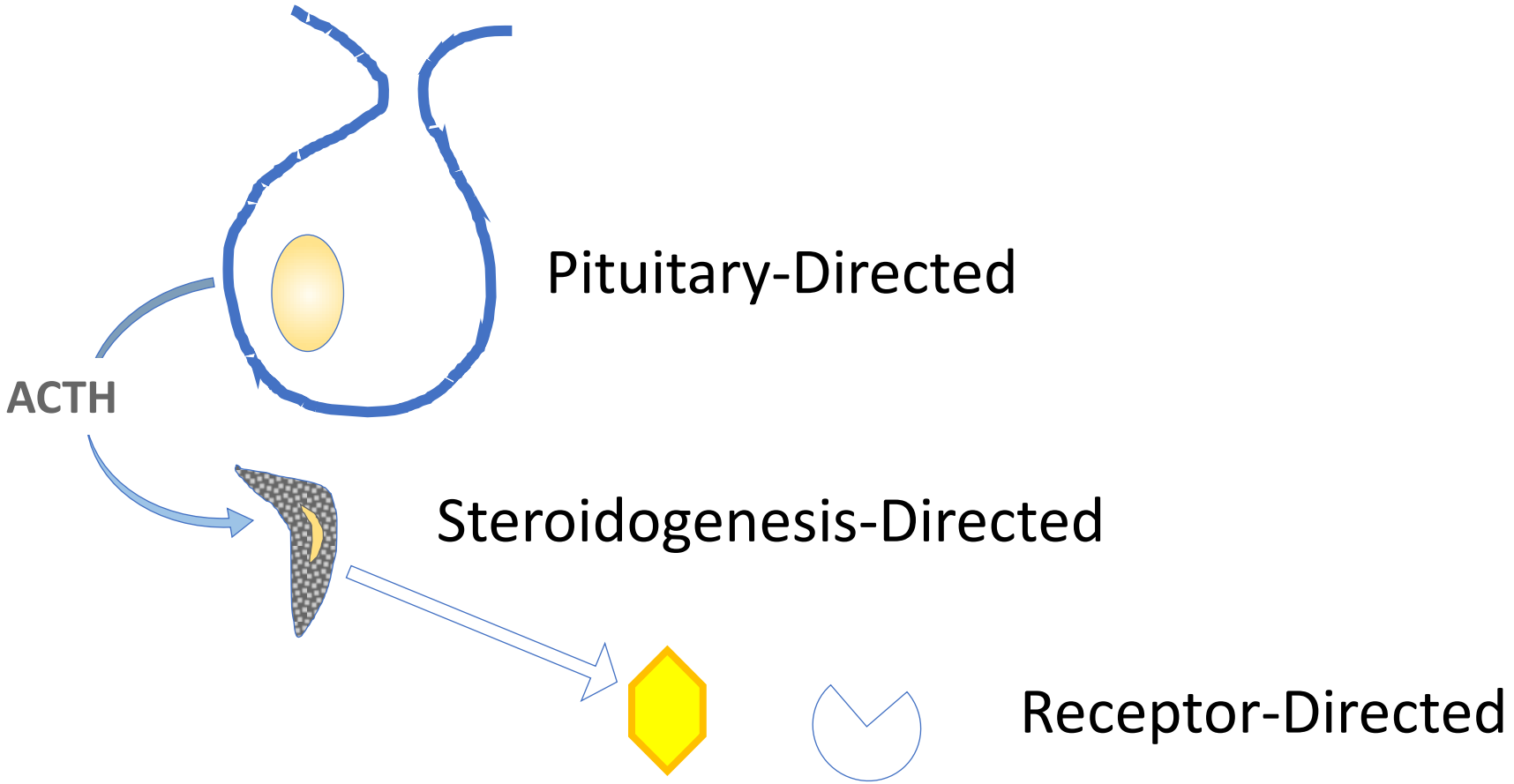
# Endocrine Society's Clinical Practice Guideline: Treatment of Cushing's syndrome

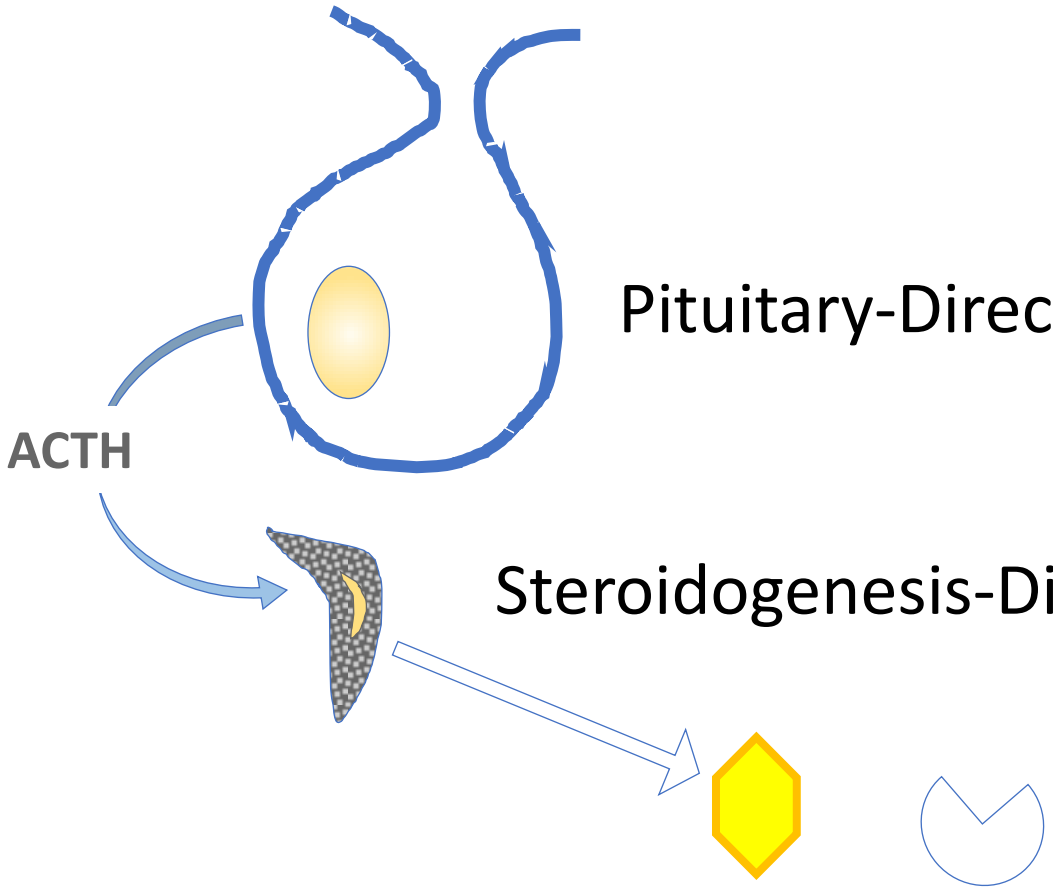



Nieman LK, et al. J Clin Endocrinol Metab.100:2807-31, 2015.

# Medical treatment of Cushing's Syndrome



# Medical treatment of Cushing's Syndrome




Pituitary-Directed

Cabergoline
Pasireotide

Steroidogenesis-Directed

Old:
Ketoconazole
Metyrapone
Mitotane

Coming:
Levo-keto
Osilodrostat

Receptor-Directed

Mifepristone

# Focus group questions

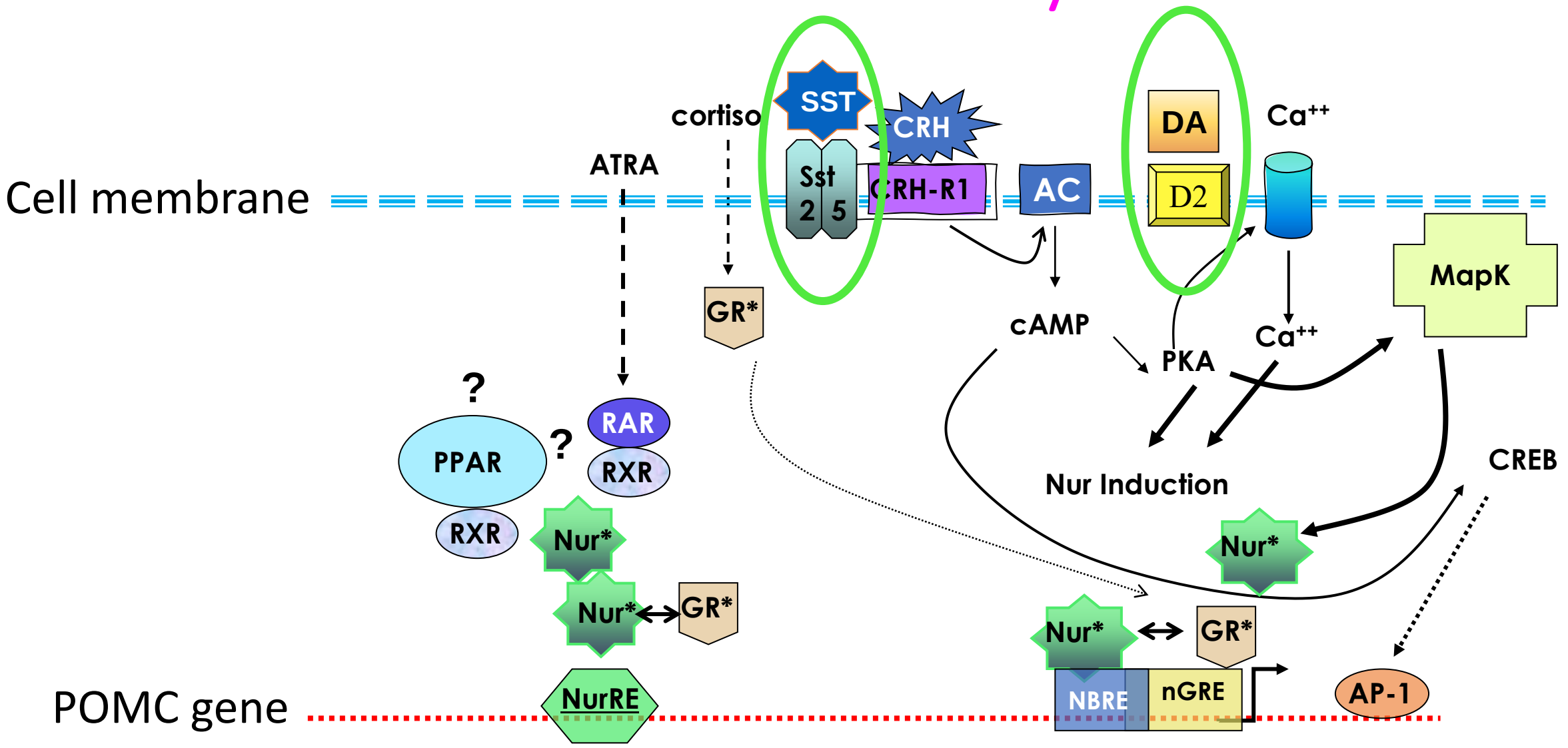
- How do drugs “get started?”
- How to find out about the drugs?
- How much experience is there with the drugs?
- How do you know there won’t be long-term toxicity?

# Focus group questions: How do drugs get started?

1. An investigator or a company has an idea, usually based on physiology, about how to reduce the amount or action of CRH, ACTH or cortisol
   - Then they work to synthesize or find such an agent
   - Test it in a cell system to find out if it has those properties
   - Test in animals
   - Apply for an investigational new drug application (IND) to the FDA/EMEA
   - Test in people
   - Publish
   - Ask agency to approve, or use is “off-label”

Examples: Levo-ketoconazole, pasireotide, mifepristone

# Pathways to discovery and practice: Interfere with POMC synthesis



# Focus group questions: How do drugs get started?

2. An investigator or a company has an idea, based an unexpected finding from a current drug
   - Then they work to identify its action on cortisol
   - Test in animals
   - Apply for an investigational new drug application (IND) to the FDA/EMEA
   - Test in people
   - Publish
   - Ask agency to approve, or use is “off-label”

Examples: ketoconazole, etomidate

# Focus group questions: How can we find out about the drugs?

- UpToDate has patient information and lists other places to find information (see handout)
- PubMed search
- Conferences
- Your doctor

# Focus group questions: How long have these drugs been around and what can I find out about them?

- Older, less expensive drugs (steroidogenesis inhibitors): more experience, but less “rigorous” studies, which may bias in favor of the drug
- Newer, more expensive drugs (pasireotide, mifepristone, cabergoline): less experience, more rigorous studies, may be less generalizable if one type of patient wasn’t included in the study trial
- ”Just approved” drug: very limited to the type and number of patients in the study(ies) and to the dose and schedule of administration

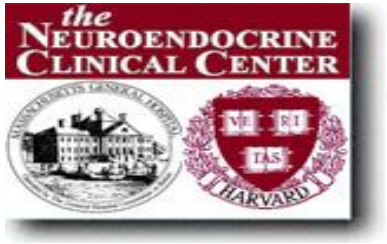
# Focus group questions: How do you know there won't be long-term toxicity?

- If used within the dose and duration of published studies, other toxicities are rare, but may occur
- If used at different doses, in a different patient, longer term, no one can really predict
- Most important calculus is the RISK:BENEFIT ratio. (Are there other treatments with equal or more likely benefit and the same or less risk?

# Older steroidogenesis inhibitors

Nicholas A Tritos, MD, DSc

October 5, 2019



# Older steroidogenesis inhibitors

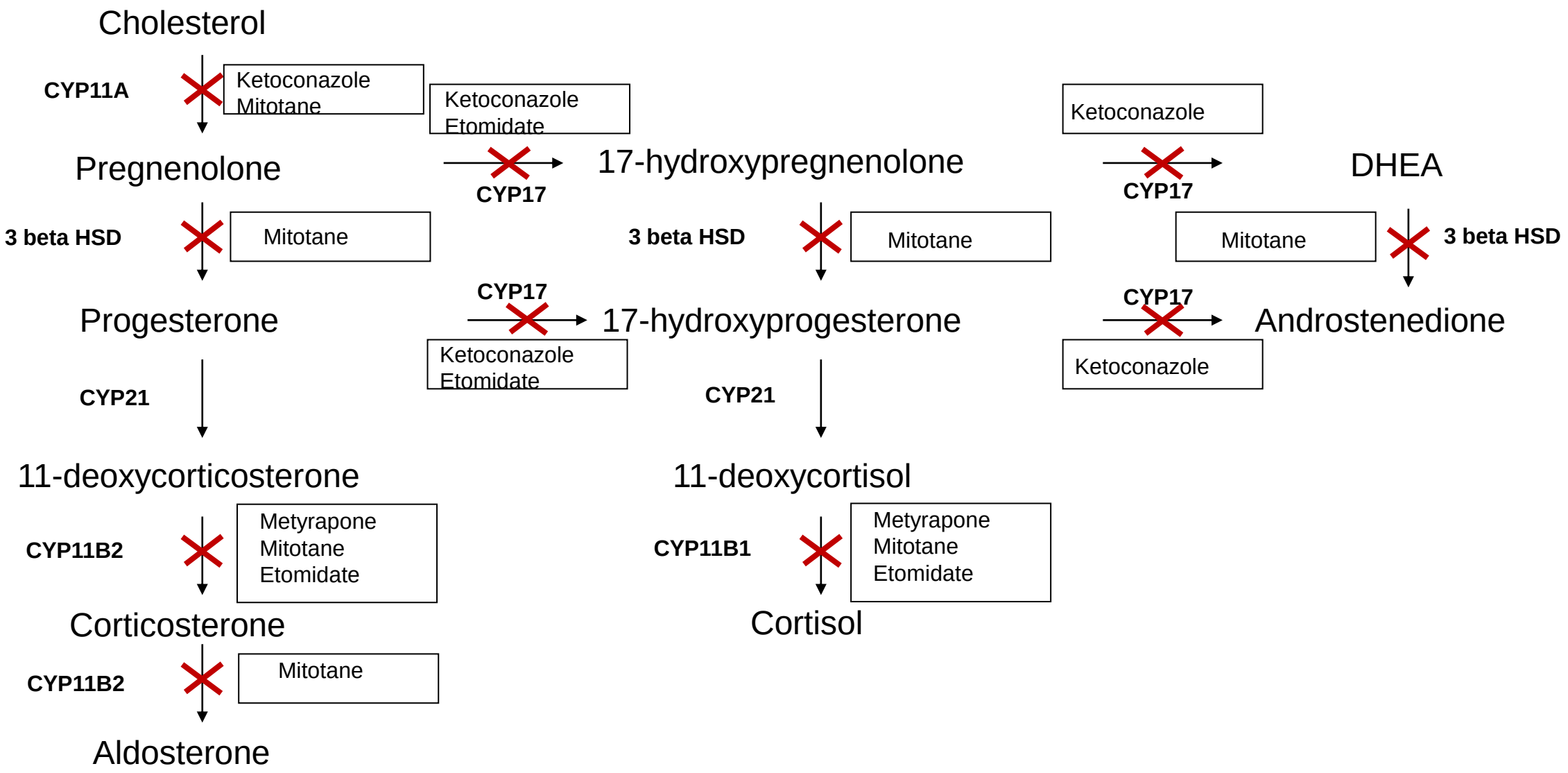
- Ketoconazole
- Metyrapone
- Mitotane
- Etomidate

How familiar are you with these medications?

# Older steroidogenesis inhibitors

- All work by blocking one or several steps involved in cortisol production by the adrenal glands
- They can be effective in controlling excess cortisol levels regardless of the tumor type that causes Cushing's syndrome; generally used as second or third line treatments (typically after surgery)
- Dose is generally adjusted towards maintaining normal 24 hour urine free cortisol (UFC)
- Some may lose effectiveness over time
- All require careful monitoring for side effects
- None are approved by the FDA for treatment of (pituitary) Cushing's disease (CD); their use is "off label" in these patients

# Mechanism of action



# Ketoconazole

How effective is it?

- In a study of 200 patients (CD) (Castinetti et al, JCEM, 2014) treated with ketoconazole at a median dose of 600 mg/day:

- 49.0% of patients had normal 24 hr urine free cortisol (UFC)
- 25.6% of patients had ≥50% improvement in UFC
- 25.4% of patients had no improvement in UFC

- 40-50% of patients showed improvements in blood pressure, diabetes mellitus and potassium levels during treatment

# Ketoconazole

How safe is it?

- In a study of 200 patients (CD) (Castinetti et al, JCEM, 2014) treated with a median dose of 600 mg/day:

- 41 patients (20.5%) stopped it because of side effects

- Mild liver inflammation (hepatitis) occurred in 13.5% of patients
- More severe liver inflammation occurred in 2.5% of patients
- No fatal hepatitis

- Other side effects include: upset stomach, adrenal insufficiency, skin itching, low testosterone (men)

# Ketoconazole

- The FDA has required the insertion of a “black box warning” in the medication label to inform patients and physicians of the potential risk of serious liver injury associated with its use
- Regular monitoring of liver function is recommended
- Potential for drug-drug interactions requires careful consideration of all medications taken concurrently

# Metyrapone

How effective is it?

- In a study of 195 patients with Cushing's syndrome (115 with CD; median dose: 1375 mg / day) (Daniel et al, JCEM, 2015) treated with metyrapone (164 patients as monotherapy) for an average duration of 8 months:

- 55% of patients had normal "cortisol day curve"
- 43% of patient had normal UFC

- Metyrapone has been used to control cortisol levels during pregnancy (not specifically labelled by the FDA for use during pregnancy)

# Metyrapone

How safe is it?

- In the same study (Daniel et al, JCEM, 2015):

- 25% of patients developed side effects
- Upset stomach and nausea in 23%
- Adrenal insufficiency in 7%

- Other possible side effects include : acne, hair growth (women), elevated blood pressure, fluid retention, low potassium levels

# Mitotane

How effective is it?

- In a study of 76 patients (CD) (Baudry et al, EJE, 2012) treated with mitotane (average dose: 2.4 g / day):

- 72% (48 out of 67) patients had normal UFC and, in fact, developed adrenal insufficiency at a median interval of 6.7 months ("remission")

- Improvements in diastolic blood pressure and glucose but increase in LDL cholesterol among patients in remission

- 71% (17 out of 24) patients observed after completion of treatment had recurrence at a median interval of 13.2 months

In the US, mitotane is used to treat adrenocortical carcinoma (not CD)

# Mitotane

How safe is it?

- In the same study (Baudry et al, EJE, 2012):

- 29% (19) patients stopped treatment because of side effects
- Nausea, vomiting, diarrhea (47.4%; serious in 6.6%)
- Liver inflammation (17.1%; serious in 1.3%)
- Neurologic (slurred speech, unsteadiness, dizziness, tingling) in 30.3% (serious in 9%)
- Elevated cholesterol or triglycerides (71.1%)
- Mildly decrease in white cell (neutrophil) count (6.6%)
- Skin rash (3.9%; serious in 6.6%)

- Teratogenic; pregnancy is not advisable for 5 years after stopping treatment

# Etomidate

How effective is it?

- In a study of 7 patients (9 “episodes”) (Carroll et al, JES, 2018) with severe Cushing’s (4 ectopic, 2 pituitary, 1 adrenocortical carcinoma) treated with etomidate (given through a vein) as “bridge treatment”:

- Cortisol levels decreased from (median) cortisol of 105 mcg/dl to 15.8 mcg/dl at a median duration of 38 hours
- Target cortisol levels were achieved in all patients (except one, who entered hospice care)

# Etomidate

How safe is it?

- In the same study (Carroll et al, JES, 2018):

- All patients were monitored in the ICU
- No patient developed excessive sedation (sleepiness)
- Two patients had nausea and vomiting

- Other possible side effects include: kidney damage, vein clot (thrombophlebitis), low blood pressure or pulse, some neurologic symptoms

# Summary

- Older steroidogenesis inhibitors are still widely used to treat (pituitary) Cushing's disease (generally as second or third line treatments) and can be effective in controlling cortisol levels in patients with all tumor types
- They can be helpful in controlling cortisol levels, particularly in patients awaiting the effects of pituitary radiotherapy
- None treat the pituitary tumor that causes the condition in Cushing's disease (mitotane is approved to treat adrenocortical carcinoma)
- All are used "off label" to lower cortisol levels and require careful monitoring
- Newer drugs under development may eventually render some of them obsolete