BIOCHEMISTRY PATHWAY SERIES FOR STEP ONE

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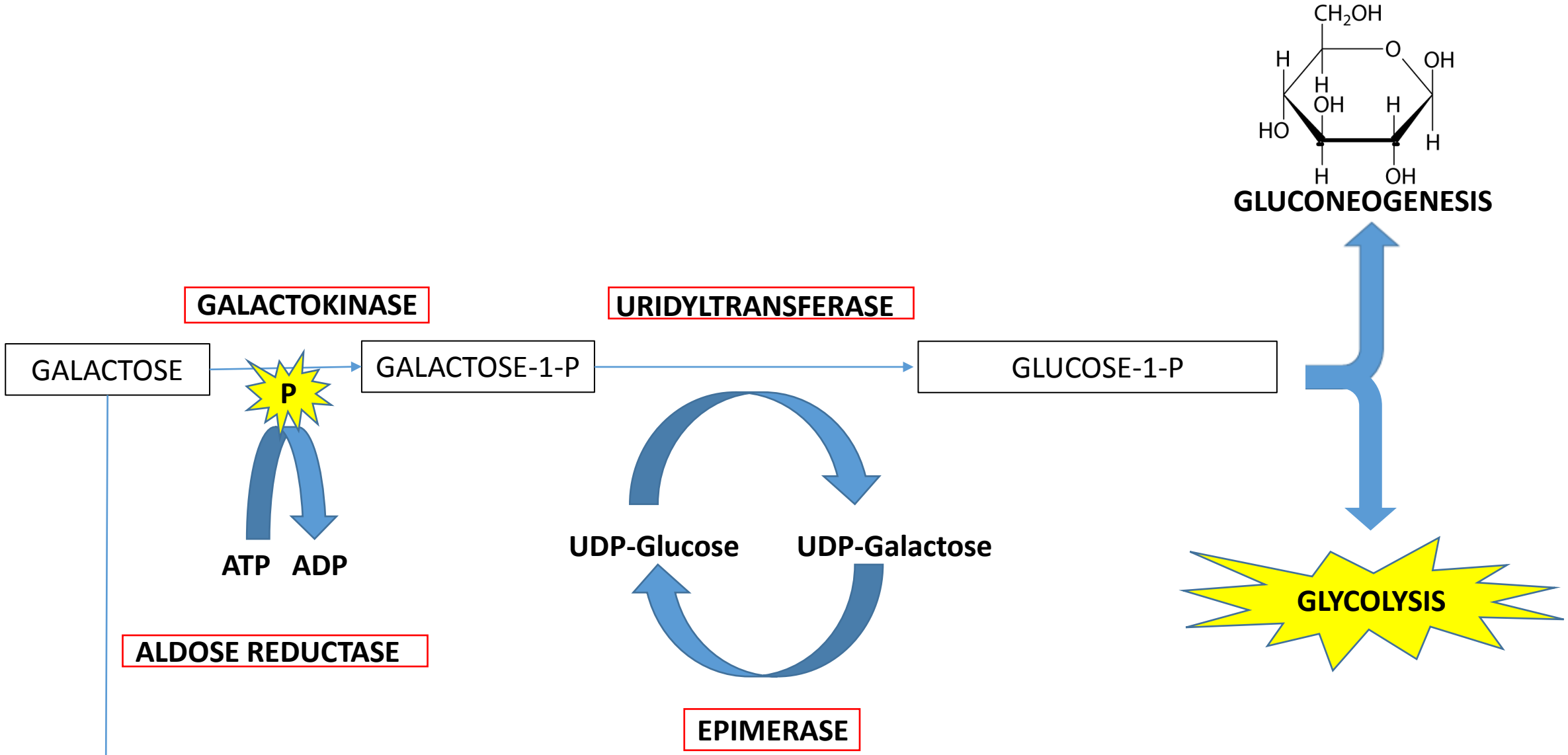
Galactose Metabolic Pathway

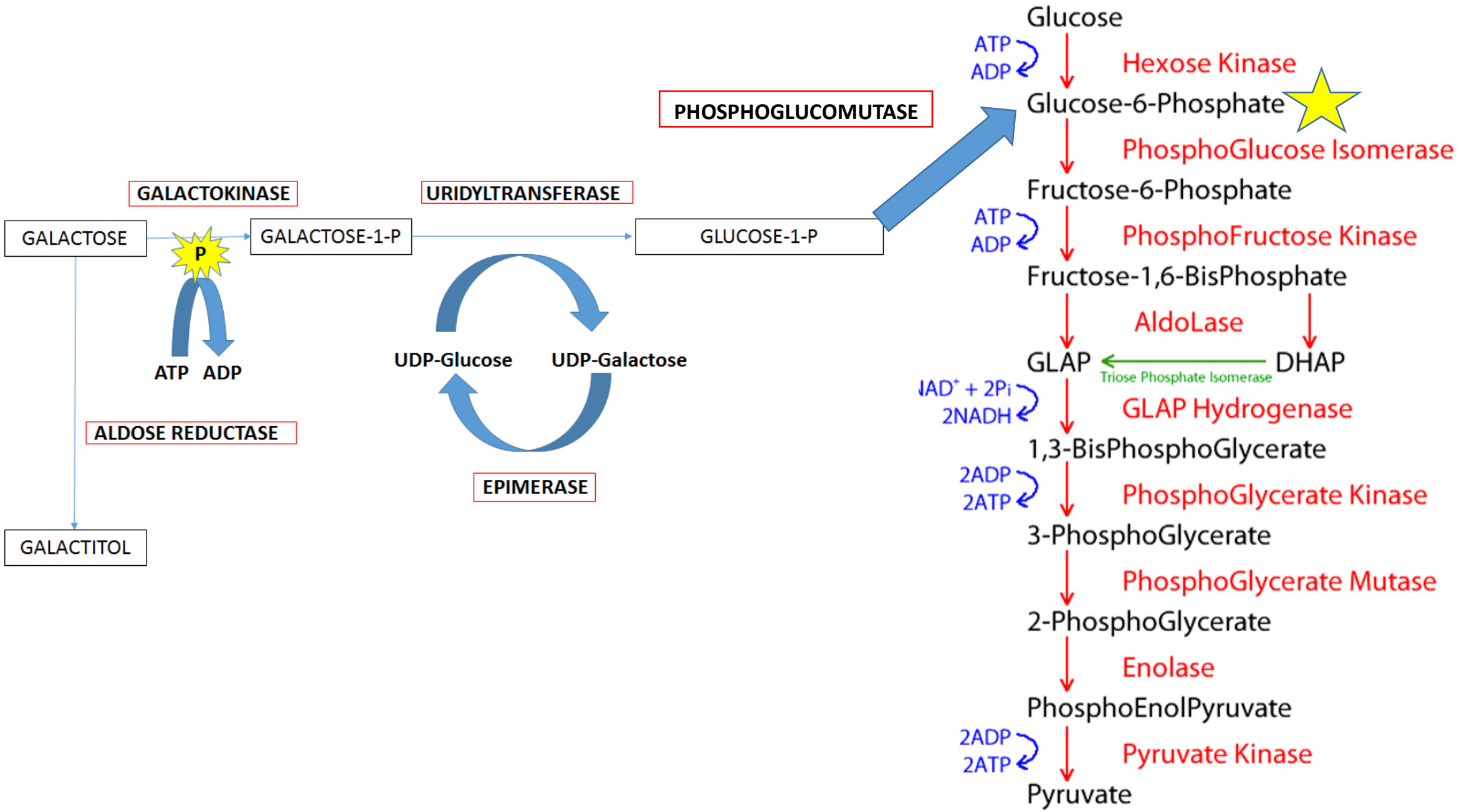
For each pathway:

- Where do we start?
- Where do we end?
- What are the goals of the pathway?
- What key enzymes will get us from start to end
- What are the key disorders related to these pathways
- How do they all come together?
- Summary: Special notes/therapeutics/key derivatives?

Galactose Metabolism

- **Start** with Galactose **end** with Glucose-1-P
- **Goal** is to generate useable energy from Galactose
- Key enzymes: **Galactokinase**, **Uridyltransferase**, **Aldose Reductase**
- Disorders: Galactokinase Deficiency, Classic Galactosemia
- Fits into pathways for gluconeogenesis, glycolysis


GALACTOSE
GALACTOKINASE
P
ATP
ADP
GALACTOSE-1-P
URIDYLTRANSFERASE
GLUCOSE-1-P
UDP-Glucose
UDP-Galactose
EPIMERASE
ALDOSE REDUCTASE
GALACTITOL
GLUCONEOGENESIS
GLYCOLYSIS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Fructose-6-Phosphate
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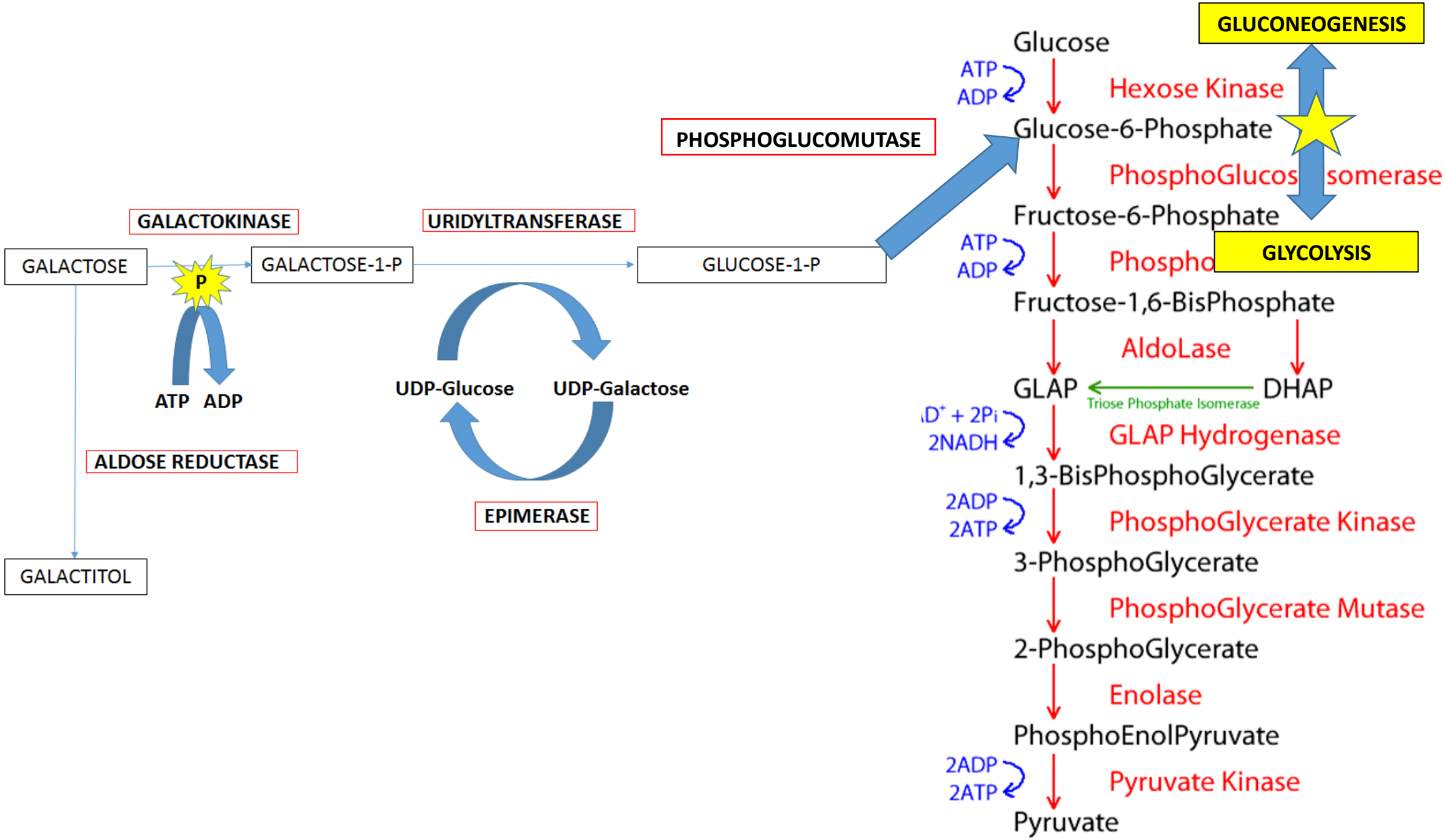
ADP
PhosphoFructose Kinase
Fructose-1,6-BisPhosphate
AldoLase
GLAP
DHAP
Triose Phosphate Isomerase
NAD+ + 2Pi
2NADH
GLAP Hydrogenase
1,3-BisPhosphoGlycerate
2ADP
2ATP
PhosphoGlycerate Kinase
3-PhosphoGlycerate
PhosphoGlycerate Mutase
2-PhosphoGlycerate
Enolase
PhosphoEnolPyruvate
2ADP
2ATP
Pyruvate Kinase
Pyruvate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Fructose-6-Phosphate
GLYCOLYSIS
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ADP
Phospho
Fructose-1,6-BisPhosphate
AldoLase
GLAP
DHAP
Triose Phosphate Isomerase
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So what's the goal?

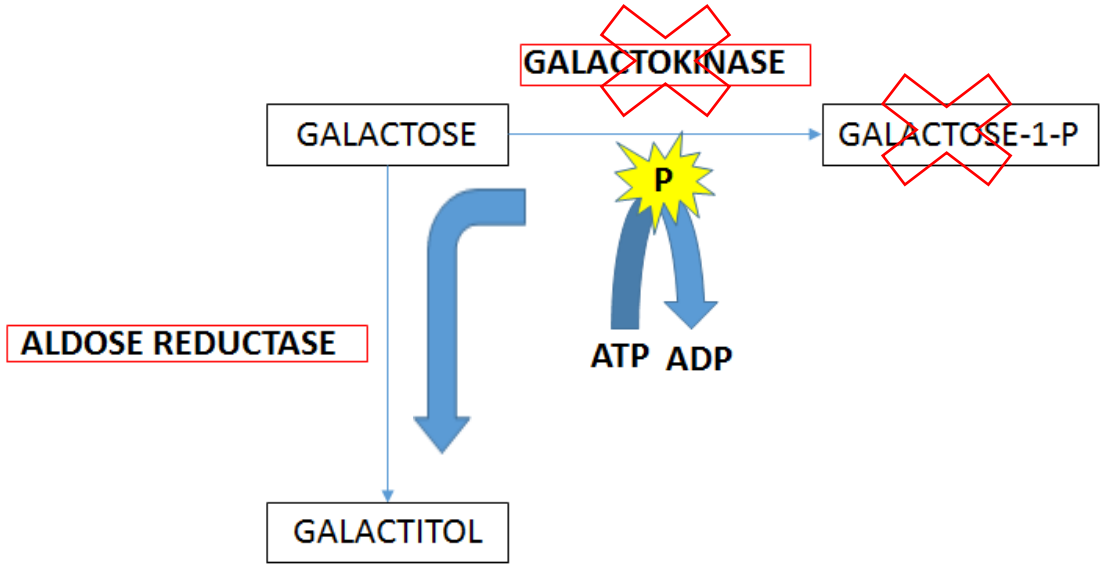
- Take a dietary sugar (galactose) and convert it into an intermediate (glucose-1P) that can be used to directly generate ATP or to produce glucose
- Problems in this pathway arise when enzymes in this pathway are **missing** or **deficient**, leading primarily to an accumulation of galactose byproducts within the cell

So what goes wrong and how does it present?

- Two important conditions associated with this pathway, each caused by a deficiency/loss of one of the key enzymes involved
- Vastly different clinical presentations
- All disorders are autosomal recessive, so if a question involves everyone in the family through multiple generations, start thinking about other pathways

Galactokinase Deficiency

- Loss of first enzyme in the pathway, which normally attaches phosphate to galactose
- This allows galactose to enter cells
- Because galactose can't enter cells, it remains in blood and urine, where it can be detected on routine testing
  - Blood → galactosemia
  - Urine → galactosuria



Galactosemia refers to galactose in blood.

This is different than Classic Galactosemia described in the next disorder

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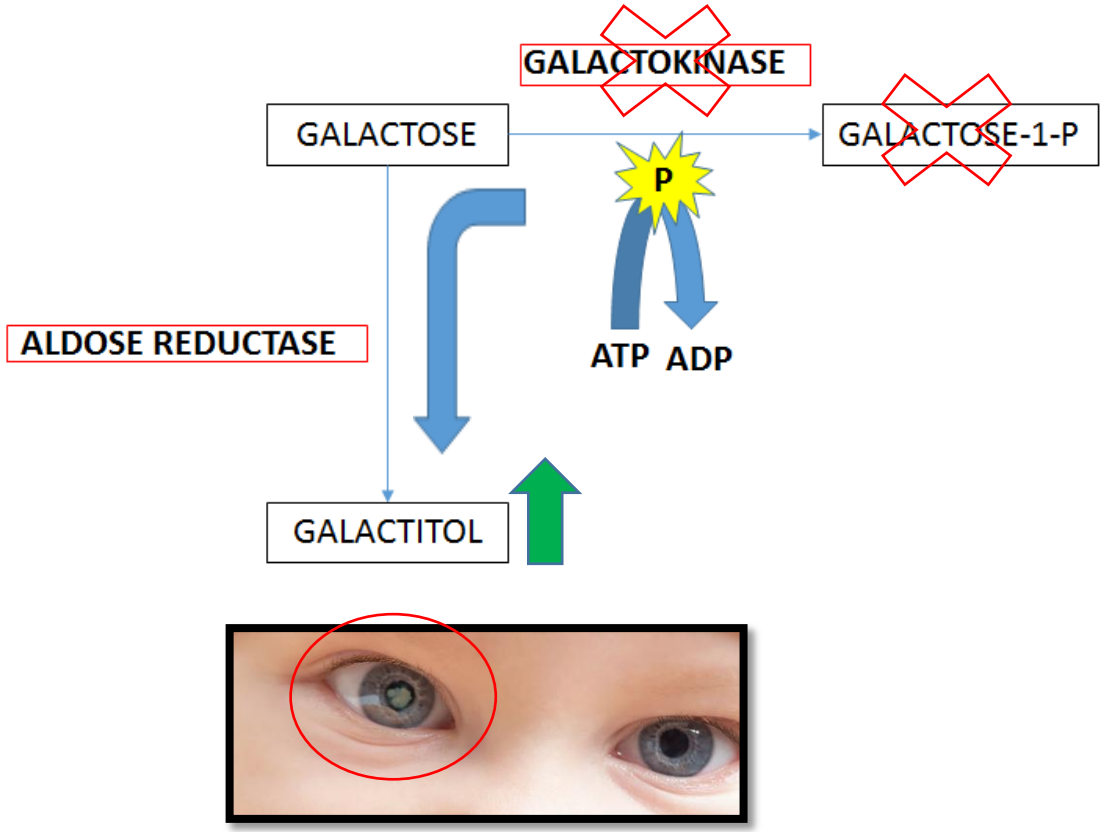
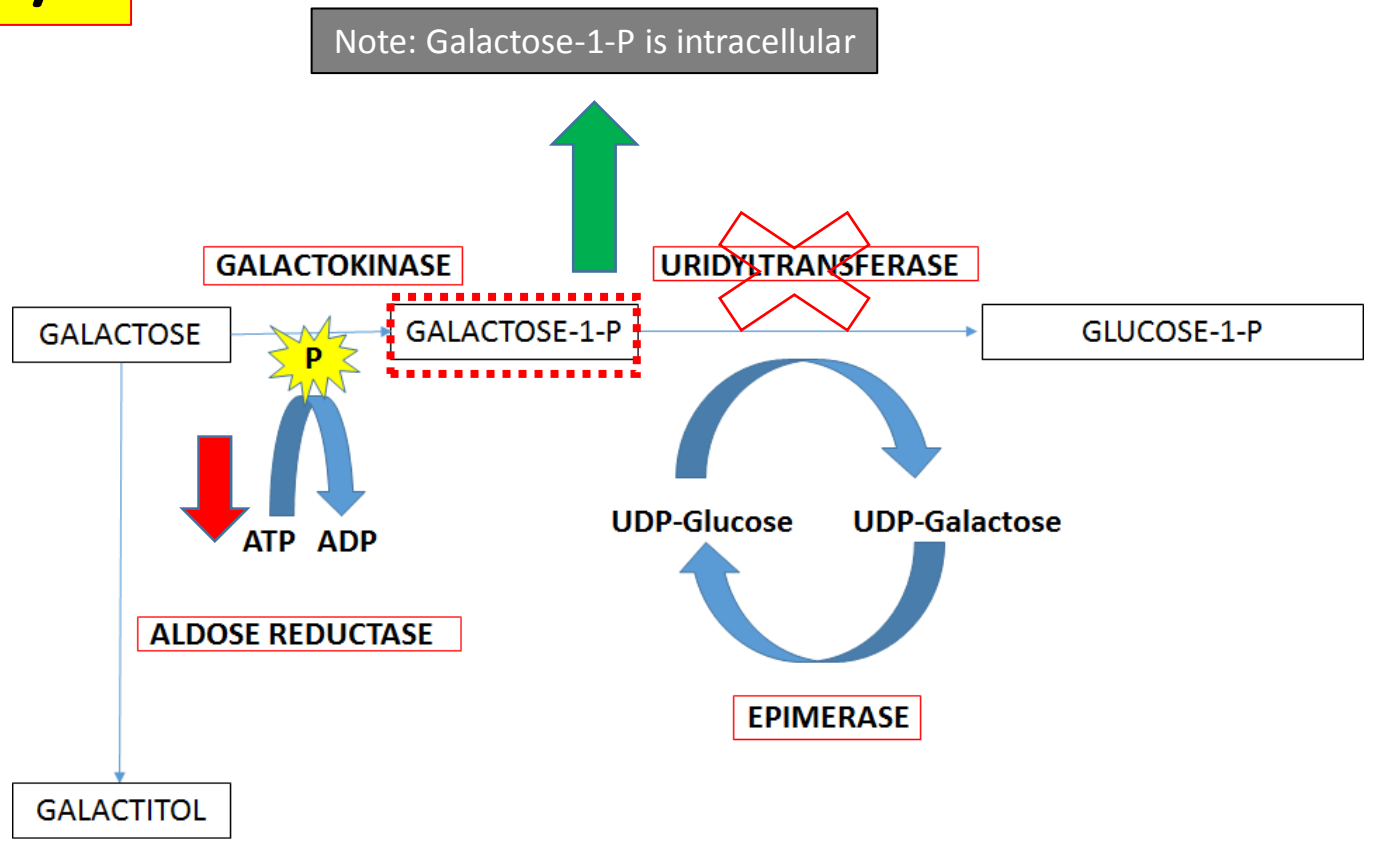
- Some galactose is converted to galactitol via **aldose reductase**
  - High levels of galactitol (like sorbitol in diabetics) is associated with infantile cataracts
- Usually detected on newborn screen.
  - If not screened symptoms usually associated with loss of vision due to cataracts → baby doesn't develop social smile, can't track objects across midline



Classic Galactosemia:
G-1-P uridyltransferase Deficiency

- Loss of second enzyme in pathway, which converts galactose-1-P to gluclose-1-P
- Galactose-1-P has **already entered the cell**, meaning if the downstream enzyme is blocked it will **accumulate**:
  - Hepatocytes don't like this.
- At the same time, galactokinase (outside the cell, oblivious to the chaos inside) is still doing its thing, endlessly burning precious ATP in the process.



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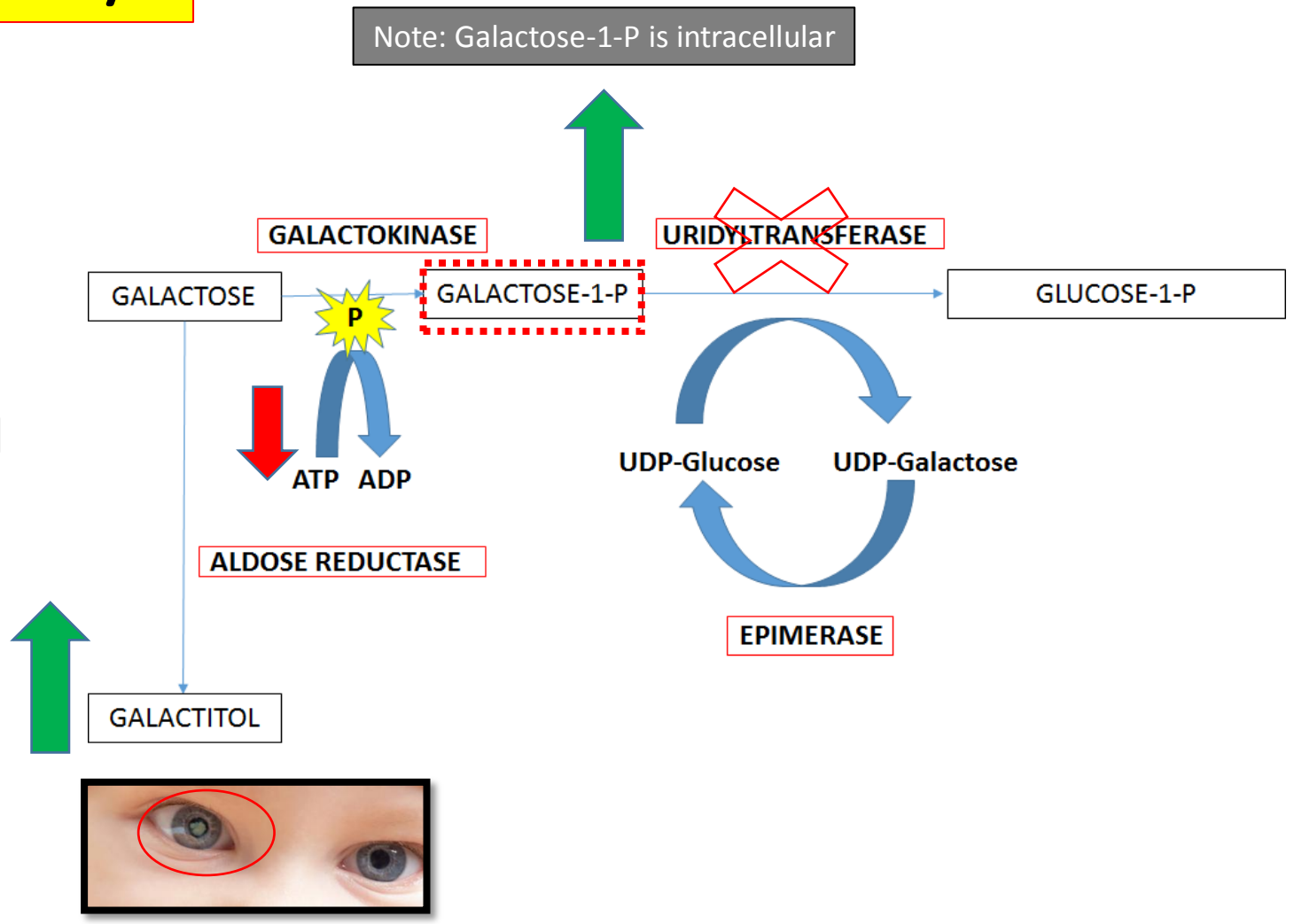
- At the same time, galactokinase (outside the cell, oblivious to the chaos inside) is still doing its thing, endlessly burning precious ATP in the process.
- There is still, however, some shunting backwards, leading to production of galactitol (remember those cataracts)
- Sxs are related to hepatocyte damage and galactitol accumulation:
  - Infantile cataracts, intellectual disability, hepatomegaly, jaundice, failure to thrive



Treatment, Tricks, and Tips

- **Treatment** for both is avoiding dietary galactose and lactose (which gets broken down to glucose and galactose)
- In the USA, these disorders are usually picked up on newborn screen. Think about these disorders if the baby is from another country or missed their newborn screen

Treatment, Tricks, and Tips

- **Treatment** for both is avoiding dietary galactose and lactose (which gets broken down to glucose and galactose)
- In the USA, these disorders are usually picked up on newborn screen. Think about these disorders if the baby is from another country or missed their newborn screen
- Tricks for remembering which disorder is associated with which enzyme:

  -Main difference in clinical picture is due to damage to **hepatocytes**. Sugars need phosphates to enter cells (usually). Kinases add phosphates. No kinases, no passage into cells, no cell damage.

  -Galactosemia is associated with loss of a kinase (i.e. galactoKINASE deficiency), therefore can't damage hepatocytes.

  -Therefore, if our baby isn't super sick (i.e. no liver involvment), it means we've lost galacto**kinase**, and have Galactosemia:

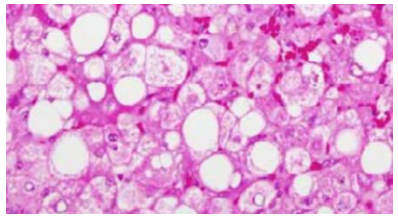
    -With Galacto**semia** I'm just not galacto**seein'ya** (because I have infantile cataracts)

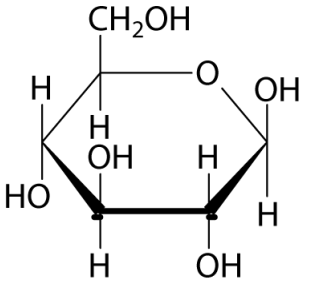
    -That was a terrible pun

For each pathway:

- Where do we start?
  - Galactose
- Where do we end?
  - Glucose-1-P
- What are the goals of the pathway?
  - Gluconeogenesis, glycolysis
- What key enzymes will get us from start to end
  - Galactokinase, Uridyltransferase; Aldose Reductase (secondarily involved when galactose accumulates)
- What are the key disorders related to these pathways
  - GalactoKINASE Deficiency with galactosemia and infantile cataracts
  - 'Classic Galactosemia': Uridyltransferase (infantile cataracts PLUS accumulation of galactose-1-P in tissue, especially liver)

The Galactose Metabolic Pathway





GLUCONEOGENESIS

GALACTOKINASE

URIDYLTRANSFERASE

GALACTOSE → (P) → GALACTOSE-1-P → GLUCOSE-1-P

ATP **ADP**

UDP-Glucose **UDP-Galactose**

EPIMERASE

GLYCOLYSIS

ALDOSE REDUCTASE

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