KU LEUVEN

RegaVir platform: Case discussions antiviral resistance testing

Robert Snoeck & Graciela Andrei

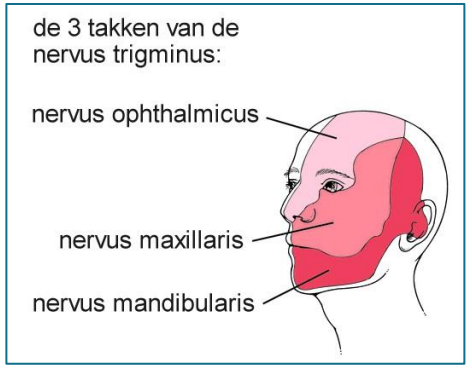
Leuven, May, 2023

Herpes Zoster Ophthalmicus (HZO)

- Patients usually present with painful, vesicular, dermatomal rashes affecting the **ophthalmic division of the trigeminal nerve (V1).**

- **The eye is affected in about half of cases of V1 varicella-zoster virus reactivation.**

- HZO acounts for 10-20% of cases of HZ infection.

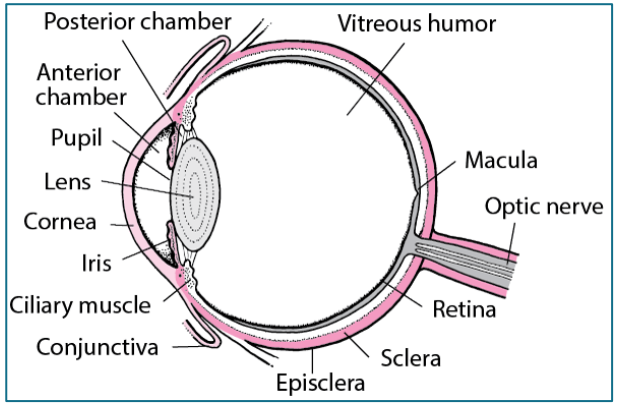


The three major sensory divisions of the trigeminal nerve

KU LEUVEN

Herpes Zoster Ophthalmicus

- **Complications:**
  - Keratitis and/or uveitis may be severe and followed by scarring.
  - Late sequelae: glaucoma, cataract, chronic or recurrent uveitis, corneal scarring, corneal neovascularization, and hypesthesia—are common and may threaten vision.
  - Postherpetic neuralgia (PHN) may develop later.
  - Patients may develop episcleritis (without increased risk of visual loss) and/or retinitis (with risk of severe visual loss).



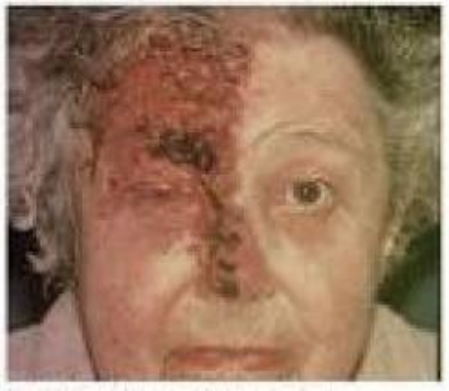
Herpes Zoster Ophthalmicus

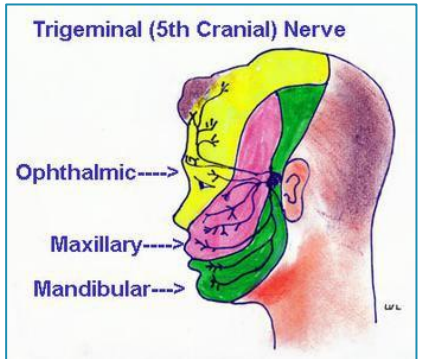
- **Treatment:**
  - ***Oral antivirals (eg, acyclovir, famciclovir, valacyclovir)***

  Early treatment with acyclovir 800 mg orally 5 times/day or famciclovir 500 mg or valacyclovir 1 g orally 3 times/day for 7 days reduces ocular complications.
  - ***Sometimes topical corticosteroids***

  Patients with uveitis or keratitis require topical corticosteroids (eg, prednisolone acetate 1%, 1 drop instilled every 1 hour for uveitis or 4 times/day for keratitis)

  - *A brief course of **high-dose oral corticosteroids** to prevent postherpetic neuralgia in patients > 60 years who are in good general health remains **controversial***





The three major sensory divisions of the trigeminal nerve

KU LEUVEN

Herpes Zoster Ophthalmicus

- **Prevention:**
  - ***Recombinant herpes zoster vaccine*** *is recommended for immunocompetent adults ≥ 50 years, regardless of whether they have had herpes zoster or been given the older, live-attenuated vaccine.*
  - ***This recombinant vaccine decreases the chance of getting herpes zoster by 97% for adults 50 to 69 years and 91% for adults ≥ 70 years.***

KU LEUVEN

	Varicella Vaccine	Herpes Zoster Vaccine	
Name	**Varivax® & Varilrix®**	**Zostavax®**	**Shingrix®**
Year of FDA licensure	1995	2006	2018
Manufacturer	Merck (Varivax®) GSK (Varilrix®)	Merck	GSK
Type	Life-attenuated viral vaccine	Life-attenuated viral vaccine	**Inactivated; Recombinant subunit**
Vaccine components	Oka strain (1350 PFU)	Oka strain (19,400 PFU)	VZV glycoprotein E (gE)
Number of doses administered	Routine 2-dose vaccination	1 dose	2 doses (2–6 months apart)
Storage	Freezer	Freezer	Refrigerator
Diluent	Sterile water	Sterile water	Adjuvant
Dose form	0.5 mL vial for intramuscular injection	0.65 mL vial for subcutaneous injection	0.5 mL vial for intramuscular injection
Recommended age	•≥ children 12 months •Adults without evidence of immunity to varicella	FDA approved: ≥50 years old CDC recommendation: ≥60 years old	FDA approved: ≥50 years old CDC rec
Efficacy	About 98% protection in children and about 75% protection in teenagers and adults	Shingles prevention •Age 50–59: 69% •Age 60–69: 64% •Age 70–79: 41% •Age ≥80: 18% efficacy PHN protection •Age 60–69: 51% •Age 70–79: 64% •Age ≥80: 41% •Overall: 51%	Shingles prevention •Age 50–59: 97.2% •Age 60–69: 96.6% •Age 70–79: 91.3% •Age ≥80: 91.4% PHN protection •Age ≥ 50: 91.2% •Age ≥ 70: 88.8%

	Varicella Vaccine	Herpes Zoster Vaccine	
Name	**Varivax® & Varilrix®**	**Zostavax®**	**Shingrix®**
Immunity duration	Unknown; however, long-term efficacy studies have demonstrated continued protection up to 10 years after vaccination	Age-dependent	Age-dependent
Contraindications	• People with a history of severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine • Immunocompromised patients • Individuals with family history of congenital immunodeficiency's • Pregnant and breastfeeding women	• People with a history of severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine • Immunocompromised patients • Individuals with family history of congenital immunodeficiency's • Pregnant and breastfeeding women	• Individuals with a history of severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or after a previous dose of Shingrix. • Pregnant and breastfeeding women • Persons who currently have shingles
Possible side effects	Most commonly: • Fever • Pain, redness, and swelling at the injection site • Varicella-like rash (transmission of varicella-virus can occur)	Most commonly: • Pain, redness, and swelling at the injection site • Muscle pain • Tiredness • Headache • Shivering • Fever • Upset stomach	Most commonly: • Pain, redness, swelling, warmth or itching at the site of injection at the injection site • Headach

Impact of recombinant zoster vaccine for prevention of herpes zoster in immunocompromised patients

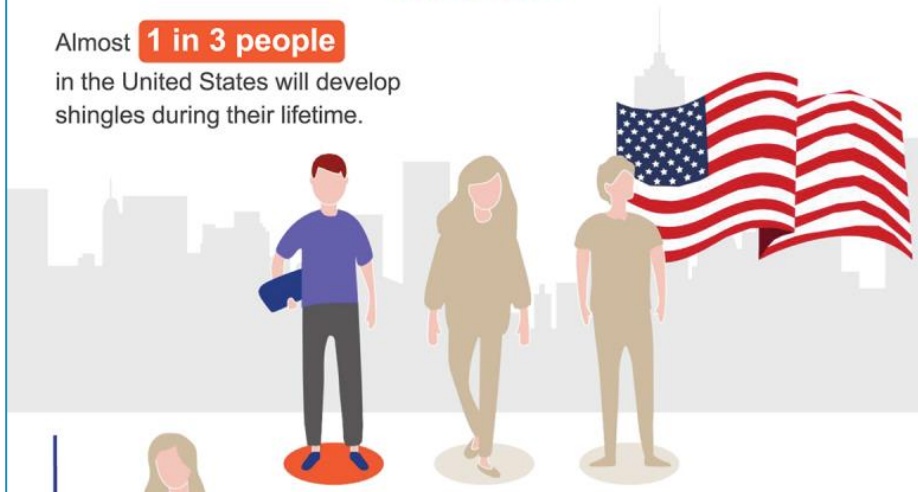
- *D. Curran et al, Hum Vaccin Immunother. 2023; 19(1): 2167907*

  - Evaluated the public health **impact of recombinant zoster vaccine (RZV) relative to no HZ vaccination for the prevention of HZ** among adults aged ≥18 years diagnosed with selected cancers in US.

  - **RZV vaccination may be an effective option to significantly reduce HZ disease burden among patients diagnosed with selected cancers in the US.**

Background

Almost **1 in 3 people** in the United States will develop shingles during their lifetime.



Shingles is characterized by a painful rash. In some people, it leads to a **persistent pain in the nerves** that can last for **months or years** after the rash is gone. This pain is called **postherpetic neuralgia**.

People who are **immunocompromised (IC) due to disease or therapy** are more likely to develop shingles. Therefore, **people with cancer** have higher rates of shingles and shingles-related complications than the general population.

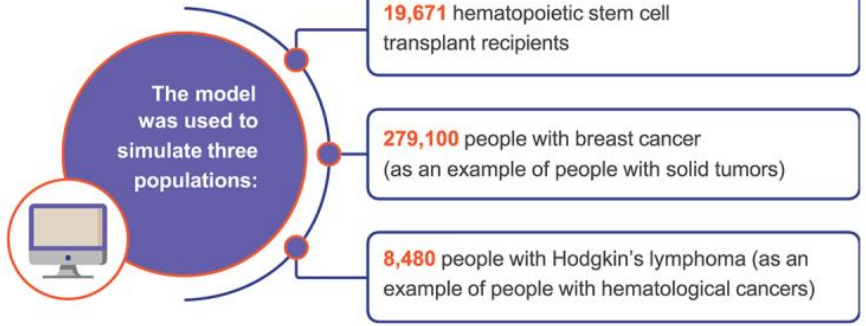
RZV* is the only vaccine available to protect against shingles in people with selected cancers.

*RZV stands for "recombinant zoster vaccine".

In October 2021, the Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control and Prevention (CDC) recommended the use of RZV for IC adults.

Aim and Method

To estimate the **public health impact** of vaccination against shingles in a population of people who are IC due to cancer, we used a model to simulate groups of IC people with selected cancers. In one scenario, these people were vaccinated with RZV, while in a second scenario, they did not receive the vaccine. The population sizes for each group are the actual population of US adults living with these conditions.



Results

Compared to no vaccination, vaccination with RZV resulted in:

	Hematopoietic stem cell transplant recipients	People with breast cancer	People with Hodgkin's lymphoma
Fewer shingles cases	↓ 38%	↓ 60%	↓ 57%
Fewer postherpetic neuralgia cases	↓ 63%	↓ 59%	↓ 73%
Fewer complication cases	↓ 41%	↓ 57%	↓ 61%
Quality-adjusted life years gained	↑ 109	↑ 506	↑ 17

In Summary

These results indicate that RZV vaccination can significantly reduce shingles cases and related complications among people with certain types of cancer in the United States.

D. Curran et al, Hum Vaccin Immunother. 2023; 19(1): 2167907

KU LEUVEN

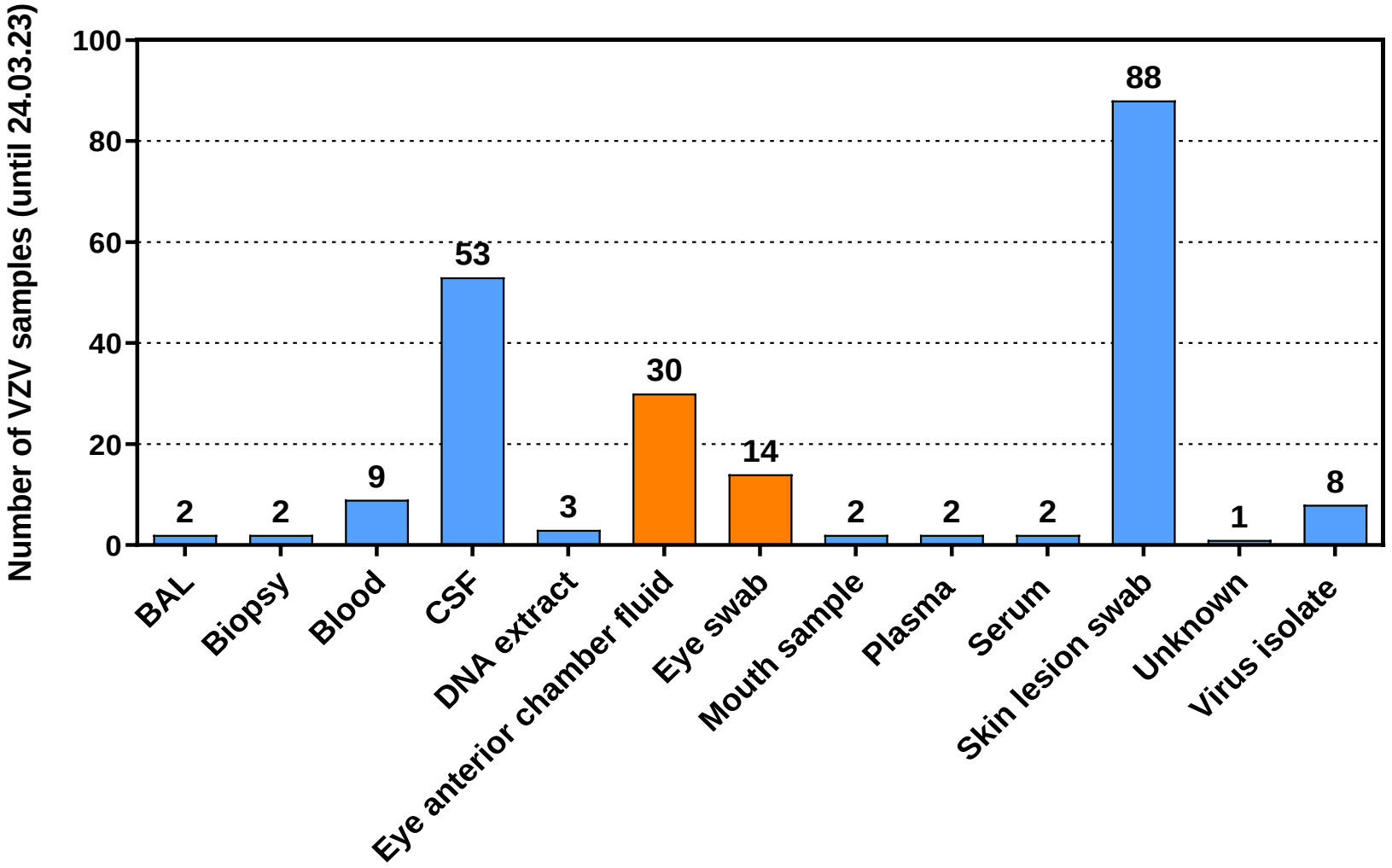
Ocular VZV complications

- VZV retinal disease: VZV produces retinal perivasculitis and various forms of necrotizing retinopathy such as:
  - Acute retinal necrosis (ARN)
    - **more common in immunocompetent patients** but can also occur in immunocompromised patients
    - characterized by necrosis (tissue death) of the retina, with the presence of a **high degree of inflammation in the eye**.
    - symptoms can include eye pain, light sensitivity, eye floaters and flashes, loss of visual clarity, blurred vision, or a narrowed visual field.
    - **The condition can lead to retinal detachment, vision loss, and blindness if untreated.**

Ocular VZV complications

- VZV retinal disease: VZV produces retinal perivasculitis and various forms of necrotizing retinopathy such as:
  - Progressive outer retinal necrosis (PORN)
    - **more common in immunosuppressed patients**
    - characterized by necrosis (tissue death) of the outer layers of the retina, with the presence of a **minimal amount of inflammation in the eye**.
    - symptoms can include eye floaters and flashes, loss of visual clarity, blurred vision, or a narrowed visual field. Eye pain and light sensitivity are usually absent.
    - **the condition progresses very rapidly to involve the entire retina and often leads to retinal detachment, vision loss, and blindness if untreated.**

Types of VZV samples analyzed by RegaVir (n=215)



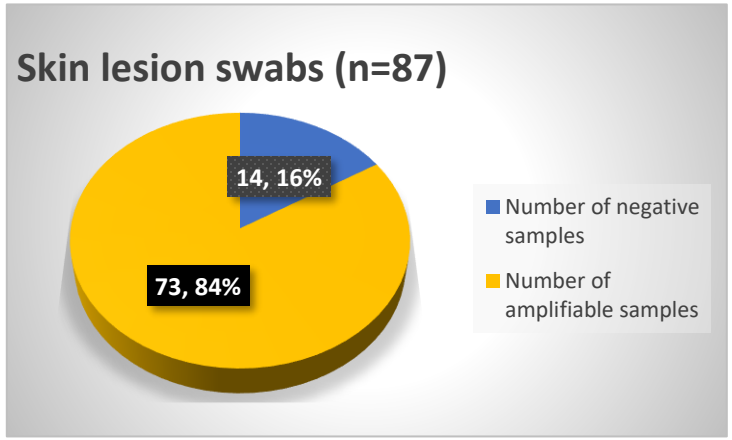
KU LEUVEN

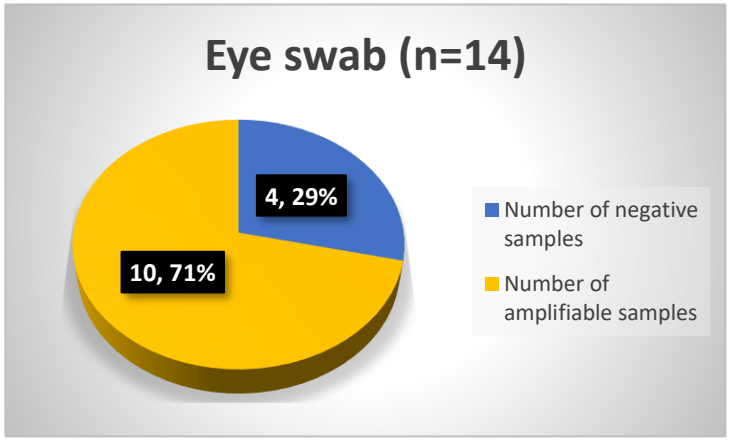
VZV samples analyzed by RegaVir (n=216)

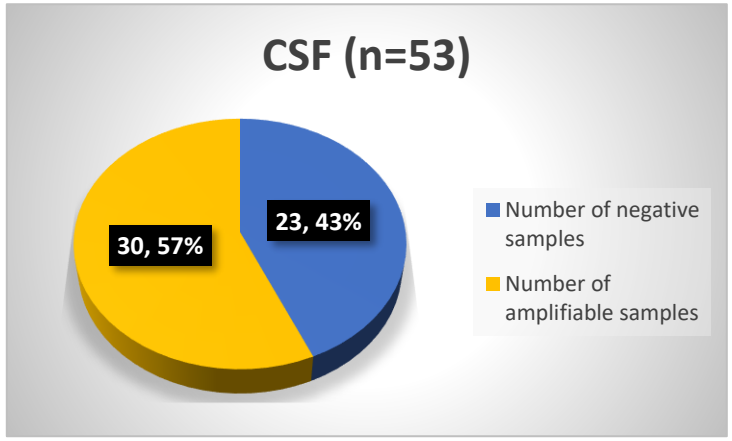
Type of samples	Number of total samples	Number of negative samples	Number of amplifiable samples
BAL	2	1	1
Biopsy	2	0	2
Blood	9	4	5
CSF	**53**	**23**	**30**
DNA extract	3	2	1
Eye anterior chamber fluid	**30**	**17**	**13**
Eye swab	**14**	**4**	**10**
Mouth sample	2	0	2
Plasma	2	0	2
Serum	2	1	1
Skin lesion swab	**87**	**14**	**73**
Unknown	1	1	1
Virus isolate	8	3	5
TOTAL	**216**	**70**	**146**

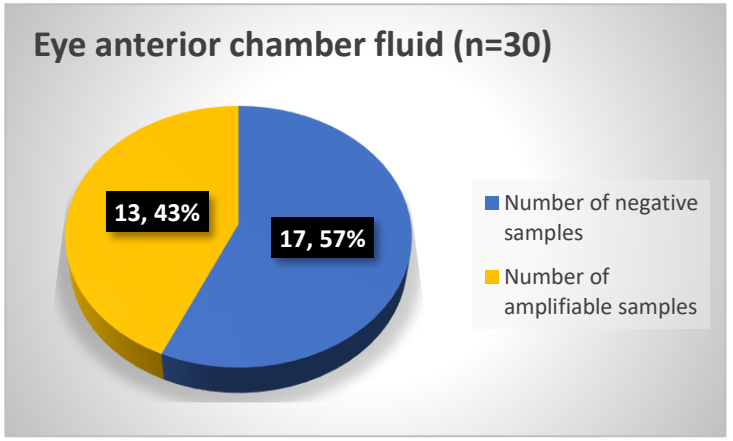
KU LEUVEN

VZV samples analyzed by RegaVir







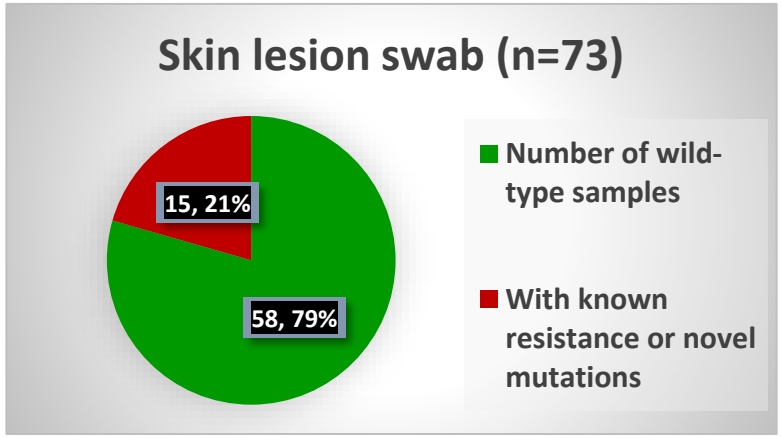


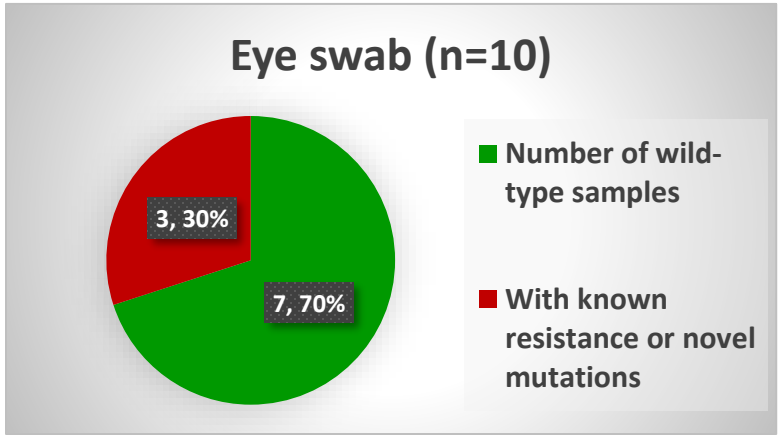
VZV **amplifiable** samples analyzed by RegaVir

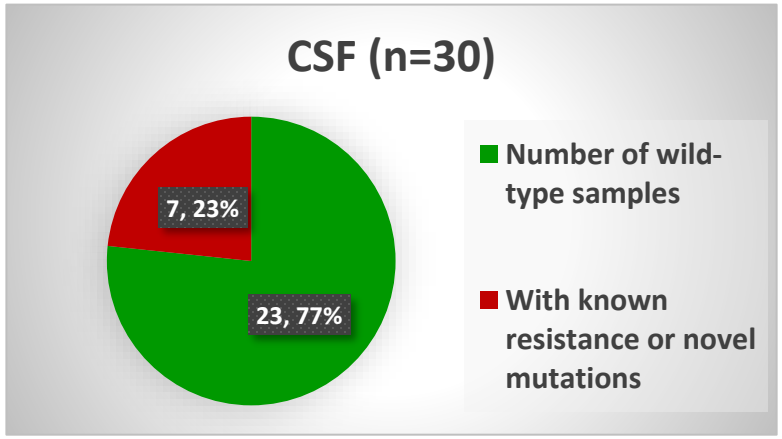
Type of samples	Number of wild-type samples	With known resistance or novel mutations
BAL	1	0
Biopsy	2	0
Blood	5	0
CSF	**23 (5 incomplete)**	**7**
DNA extract	1	0
Eye anterior chamber fluid	**9 (4 incomplete)**	**4**
Eye swab	**7**	**3**
Mouth sample	1	1
Plasma	2	0
Serum	0	1
Skin lesion swab	**58 (1 incomplete)**	**15**
Unknown	1	0
Virus isolate	5	0

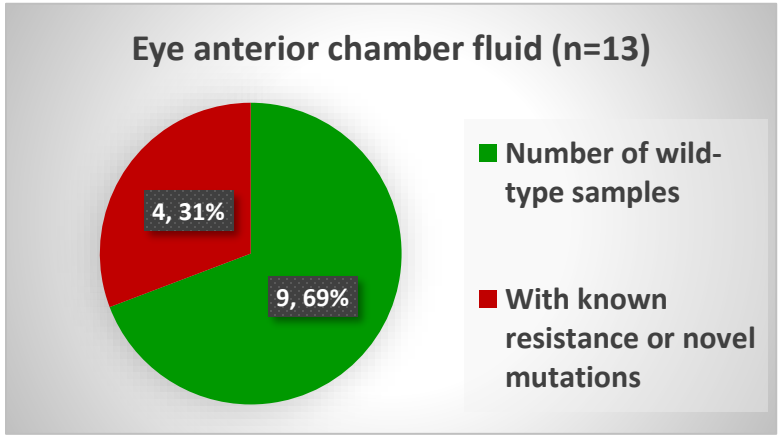
KU LEUVEN

VZV **amplifiable** samples analyzed by RegaVir

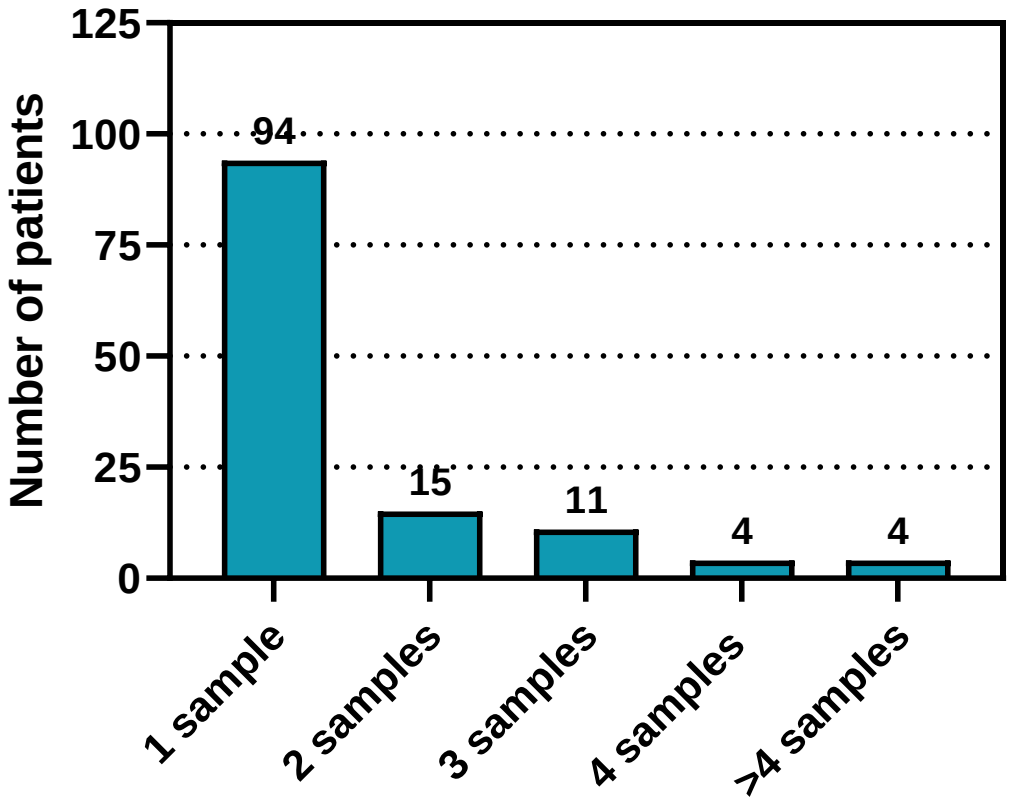




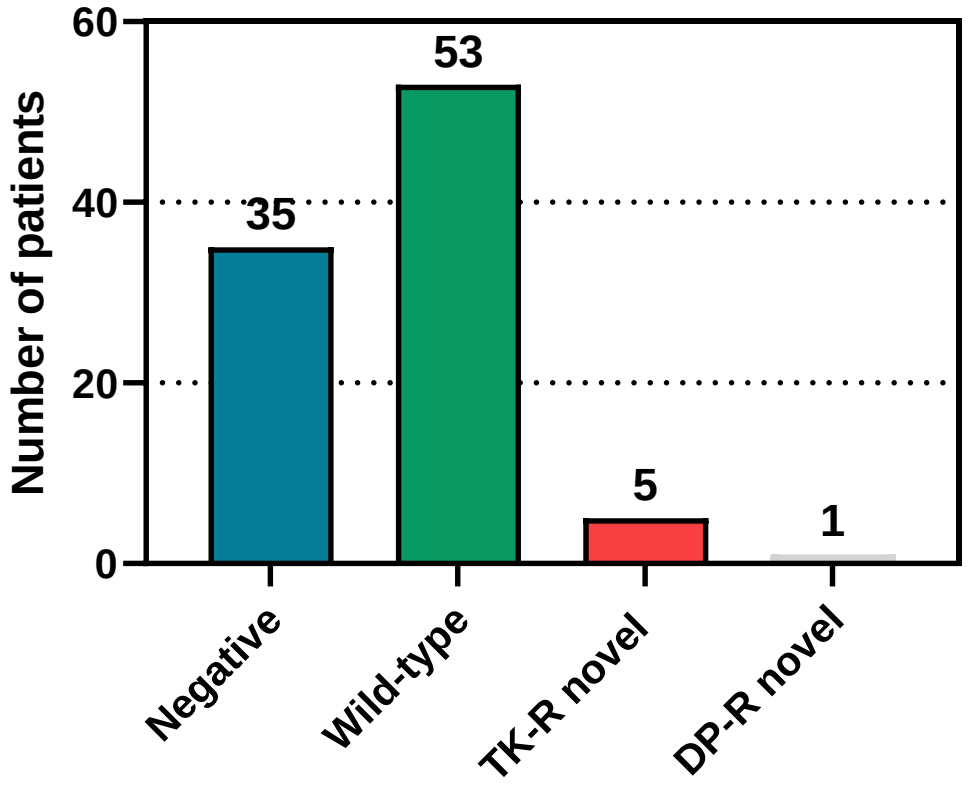




Number of patients analyzed for VZV



Number of patients with 1 VZV sample analyzed (n=94)



	Negative	Wild-type	TK-R novel	DNA pol-R novel
Biopsy	0	1	0	0
Blood	1	0	0	0
CSF	9	9	0	**1**
Eye sample	13	12	**5**	0
Serum	1	0	0	0
Swab skin lesion	10	30	0	0
Unknown	1	0	0	0
Virus isolate	0	1	0	0

KU LEUVEN

Patients with 1 VZV sample analyzed – eye complications

RegaVir ID	Hospital	Date	Type	Disease	Treatment	VZV genotyping
RV-649	Hôpital Erasme	16.04.14	Eye anterior chamber fluid (DNA extract)	Not provided	Not provided	TK novel mutation: **D38stop**
RV-1609	AZ Sint Jan Brugge-Oostende	06.11.18	Eye cornea swab	AML **Ophthalmic zoster – necrotizing ulcerative keratitis**	Prophylactic → therapeutic acyclovir	TK novel mutation: **S290G**
RV-2511	UZ Leuven	18.05.22	Eye cornea swab	**VZV keratitis** 01.03.2021 1st episode 18.05.2022 4th relapse	Prophylactic valacyclovir	TK novel mutation: **del TT 985-986**
RV-2655	UZ Leuven	22.12.22	Eye, anterior chamber fluid	**Acute retinal necrosis (ARN)**	Not provided	TK novel mutation: **F294S**
RV-2668	UZ Leuven	23.01.23	Eye, anterior chamber fluid	Lymphopenia Bilateral VZV endophthalmitis with **acute retinal necrosis (ARN)** Progression of VZV disease despite therapy	Therapeutic valacyclovir	TK novel mutation: **F294S**

KU LEUVEN

Patients with ≥2 samples VZV sample analyzed – eye complications

- Patient (UZ Gent) – retinitis, retinal necrosis on left eye – multi-treated (valacyclovir, acyclovir, foscarnet)
  - ➢ **4 non-amplifiable samples (eye anterior chamber fluid)**

- Patient (Hôpital de la Croix Rousse; Lyon): herpes zoster ophthalmicus – VZV necrotic retinitis
  - ➢ **2 non-amplifiable samples (eye anterior chamber fluid)**

Patients with ≥2 samples VZV sample analyzed – eye complications

- Patient (West Virginia University): herpes zoster ophthalmicus – retinitis, retinal necrosis on left eye

			Amino acid changes in ORF36 (thymidine kinase): 341 amino acids (complete sequence)			Amino acid changes in ORF28 (DNA polymerase): 1194 amino acids (complete)	
	Date	Type	Known to be related to genetic polymorphism (inter-strain variability)	Known to be associated with resistance to antiviral drugs	Novel most likely linked to drug-R	Known to be related to genetic polymorphism (inter-strain variability)	Known to be associated with resistance to antiviral drugs
RV-52	06.10.09	Swab	None	None	**L257S**	C186G E762D G863S R1159C	None
RV-59	06.11.09	Eye swab	None	None	**L257S**	C186G E762D G863S R1159C	None

Patients with ≥2 samples VZV sample analyzed – eye complications

- Patient (UZ Leuven) – Acute retinal necrosis (ARN) – therapeutic valacyclovir 3x/d 1g + intravitreal foscarnet (0.1 ml = 2.4mg)

			Amino acid changes in ORF36 (thymidine kinase): 341 amino acids		**Amino acid changes in ORF28 (DNA polymerase): 1194 amino acids**	
	Date	Type	Known to be related to genetic polymorphism (inter-strain variability)	Known to be associated with resistance to antiviral drugs	Known to be related to genetic polymorphism (inter-strain variability)	Known to be associated with resistance to antiviral drugs
RV-1648 (before therapy)	21.08.18	Anterior chamber fluid	None (incomplete)	None (incomplete)	None (all positions verified)	None (all positions verified)
RV-1663 (under therapy)	06.11.09	Anterior chamber fluid	None (incomplete)	None (incomplete)	None (incomplete)	None (incomplete)

Patients with ≥2 samples VZV sample analyzed – eye complications

- Patient (UZ Gent) – T-ALL relapse – Antiviral treatment received: therapeutic acyclovir 19.09.2020 → 29.09.2020

			Amino acid changes in ORF36 (thymidine kinase): 341 amino acids		**Amino acid changes in ORF28 (DNA polymerase): 1194 amino acids**	
	Date	Type	Known to be related to genetic polymorphism (inter-strain variability)	Known to be associated with resistance to antiviral drugs	Known to be related to genetic polymorphism (inter-strain variability)	Known to be associated with resistance to antiviral drugs
RV-2140	24.09.20	Anterior chamber fluid	None (complete sequence)	None (complete sequence)	None (all positions verified)	None (all positions verified)
RV-2142	07.10.20	Eye swab	Not amplifiable	Not amplifiable	Not amplifiable	Not amplifiable

Patients with ≥2 samples VZV sample analyzed – eye complications

- Patient (AZ Sint Jan Brugge-Oostende) – anterior uveitis and corneal lesions, acute retinitis, keratitis

Acyclovir started o 5/1/2014 for anterior uveitis & corneal lesions (zona lesions?) for 14 days → stop treatment → relapse inflammation intra-ocular → DD: psoriatic lesions *versus* auto-immunity *versus* zona relapse → 5/3/2014: start: 5x 800mg/d acyclovir → 30/04/2014: start zelitrex (valacyclovir) 3x 1g/d → lesions persisting – relapse under antiviral therapy

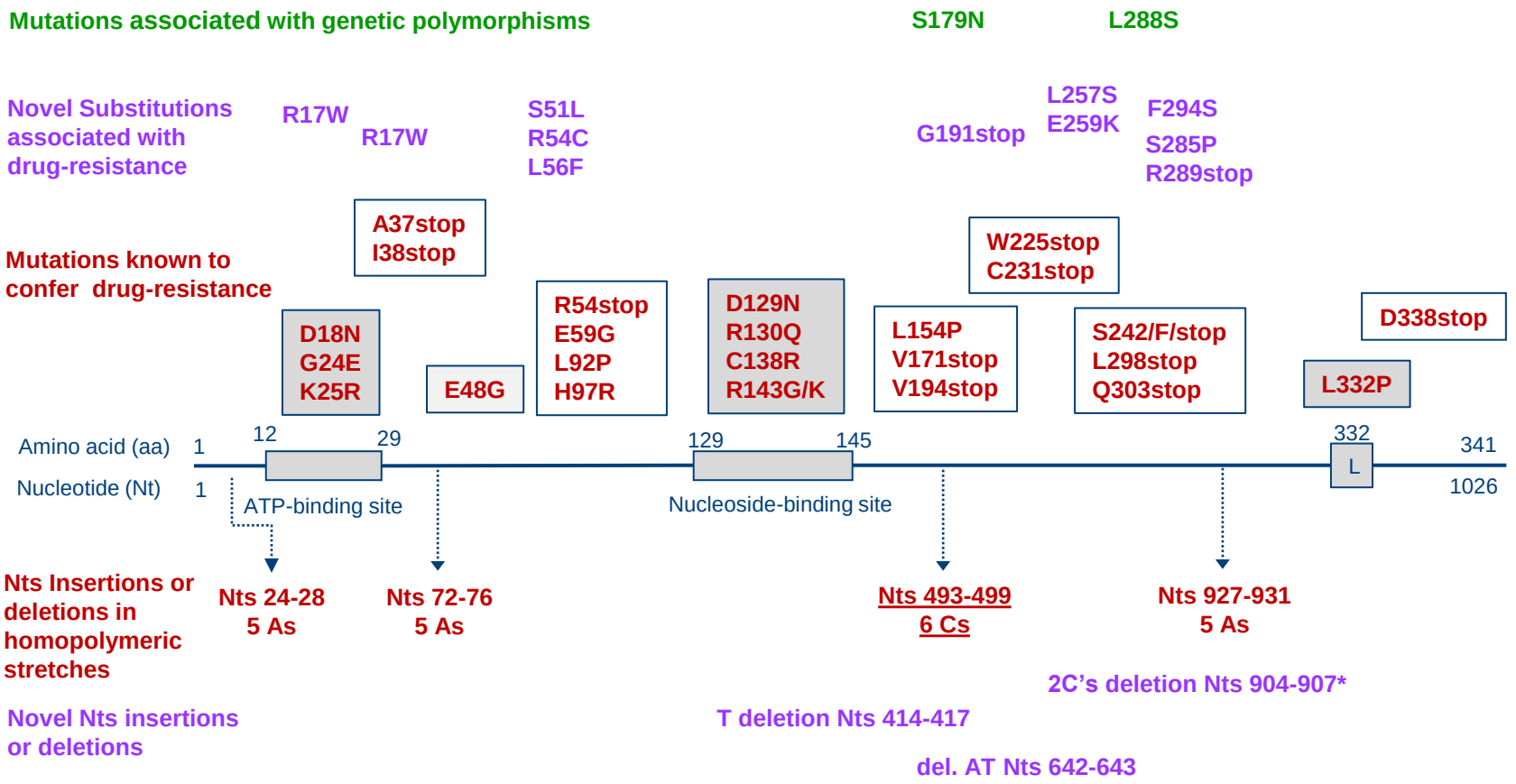
			Amino acid changes in ORF36 (thymidine kinase): 341 amino acids (complete sequence)			**Amino acid changes in ORF28 (DNA polymerase): 1194 amino acids (complete)**	
	Date	Type	Known to be related to genetic polymorphism (inter-strain variability)	Known to be associated with resistance to antiviral drugs	Novel – most likely associated with resistance to antiviral drugs	Known to be related to genetic polymorphism (inter-strain variability)	Known to be associated with resistance to antiviral drugs
RV-658	12.05.14	Anterior chamber fluid	None	None incomplete	**F32S_mixed S91G_mixed**	Not amplifiable	Not amplifiable
RV-667	05.06.14	Anterior chamber fluid	Not amplifiable	Not amplifiable	Not amplifiable	Not amplifiable	Not amplifiable
RV-715	03.09.14	Anterior chamber fluid	None	None incomplete	None	Not amplifiable	Not amplifiable

KU LEUVEN

Summary

- Patients with VZV ocular involvement should be carefully monitored for development of drug-resistance and tailored antiviral treatment.
- Risk for severe complications if non-adapted antiviral therapy is used for management of VZV ocular infections.
- Herpes zoster vaccination should be recommended to prevent shingles.

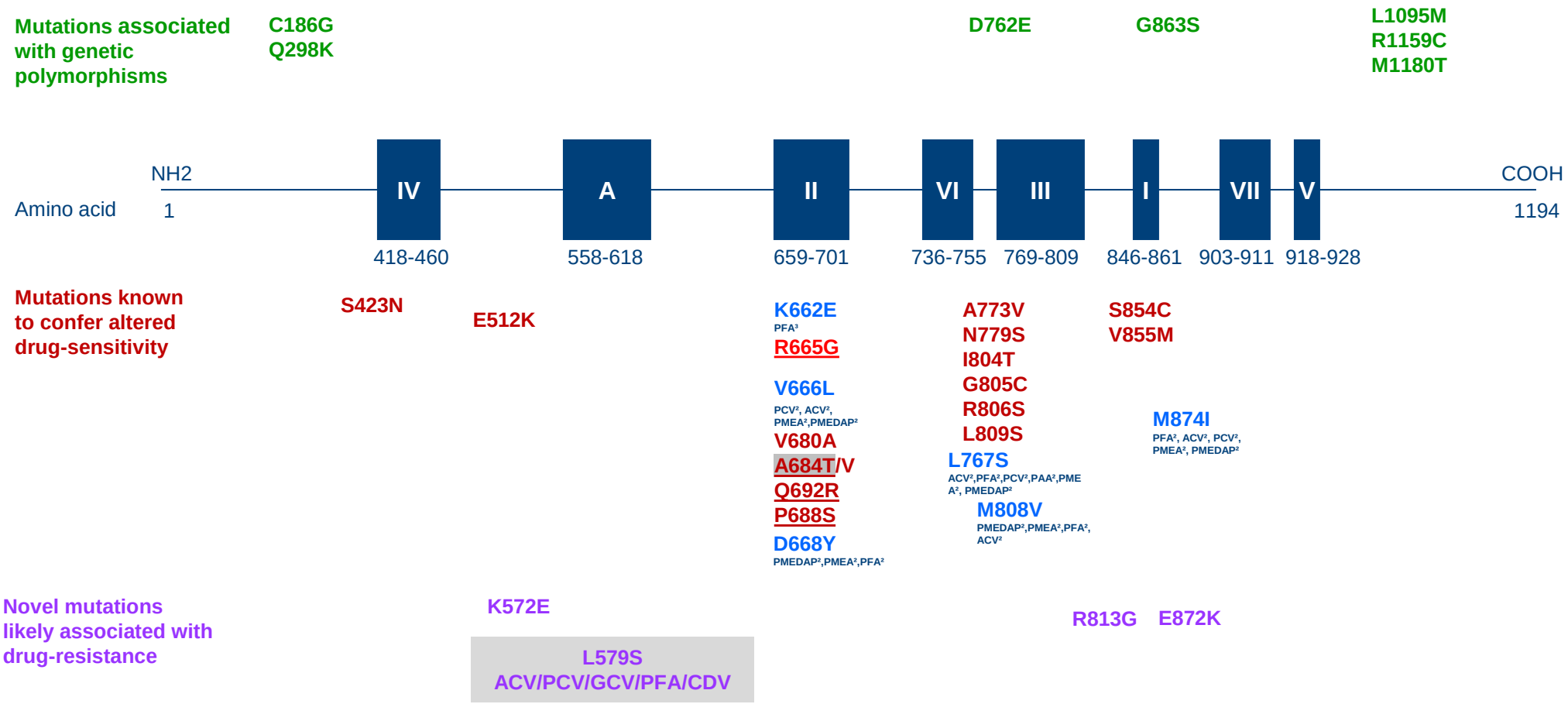
VZV thymidine kinase



Known drug-resistance mutations found by RegaVir are underlined

KU LEUVEN

VZV DNA polymerase



- ***Underlined: known drug-resistance mutations found by RegaVir***
- **Phenotyping performed**

KU LEUVEN