



DEMONSTRATING THE
POWER OF INNOVATION IN EUROPE

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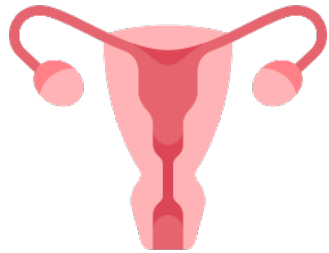
EQUALIS

strategy & modeling

VINTURA

Case study deep dives

1



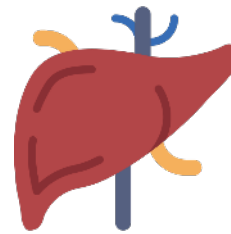
HPV vaccination to prevent cervical cancer

2



Allowing RA patients to live a normal life with biologics

3



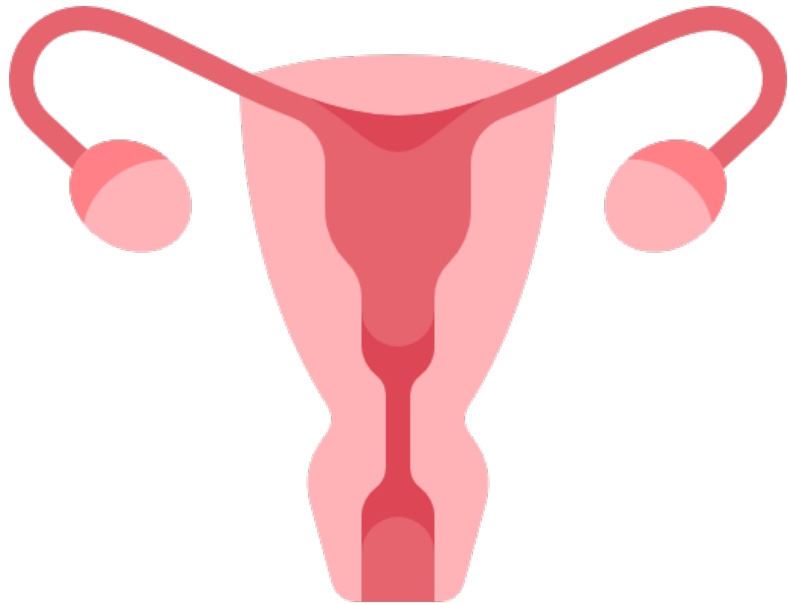
The DAAs: a paradigm shift in chronic Hepatitis C treatment

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Immuno- & targeted therapy saving melanoma patient lives

HPV vaccination to prevent cervical cancer



CASE OUTLINE

I. Case for change

- *Situation*
- *Challenge*
- *Paradigm shift*
- *Patient population*

II. Value to patients

III. Value to the healthcare system

IV. Value to society

V. Annex

- *Key assumptions*
- *Reference list*

Case summary | Cervical Cancer Vaccines

HPV vaccination to prevent cervical cancer

CASE FOR CHANGE



- **Situation** – Cervical cancer is a type of cancer that is found in the cervix, and primarily affects women of working age. Treatment for cervical cancer includes surgery, chemotherapy, radiotherapy and brachytherapy
- **Challenge** – Cervical cancer has a major impact on patients, the healthcare system, and society. Current estimates indicate that, in EU27, more than 30,000 women are diagnosed with cervical cancer and around 13,500 die from the disease every year
- **Paradigm shift** – Almost all ($\geq 95\%$) cases of cervical cancer are caused by an infection from human papillomavirus (HPV). Since 2006, several vaccines against HPV have become available in the EU27, providing the opportunity to prevent most cases of cervical cancer
- **Population** – In the EU27, every year, over 2.2 M 12-year-old girls become eligible for HPV vaccination and can benefit from its protection throughout their lives

VALUE FOR PATIENTS



- **Preventable cases and deaths** – More than 27,000 cervical cancer cases and 12,000 deaths can be prevented by HPV vaccination, each year
- **Preventable diagnostic wait time / events** – Each year, over 19M women are invited to be screened for HPV. Screening and testing can cause discomfort and stress. Screened women all wait 2-6 weeks in uncertainty for the results of a diagnostic test for cervical cancer. The burden of cervical cancer screening can be reduced by 57% with HPV vaccination, as vaccinated women require less screening

VALUE TO THE HEALTHCARE SYSTEM



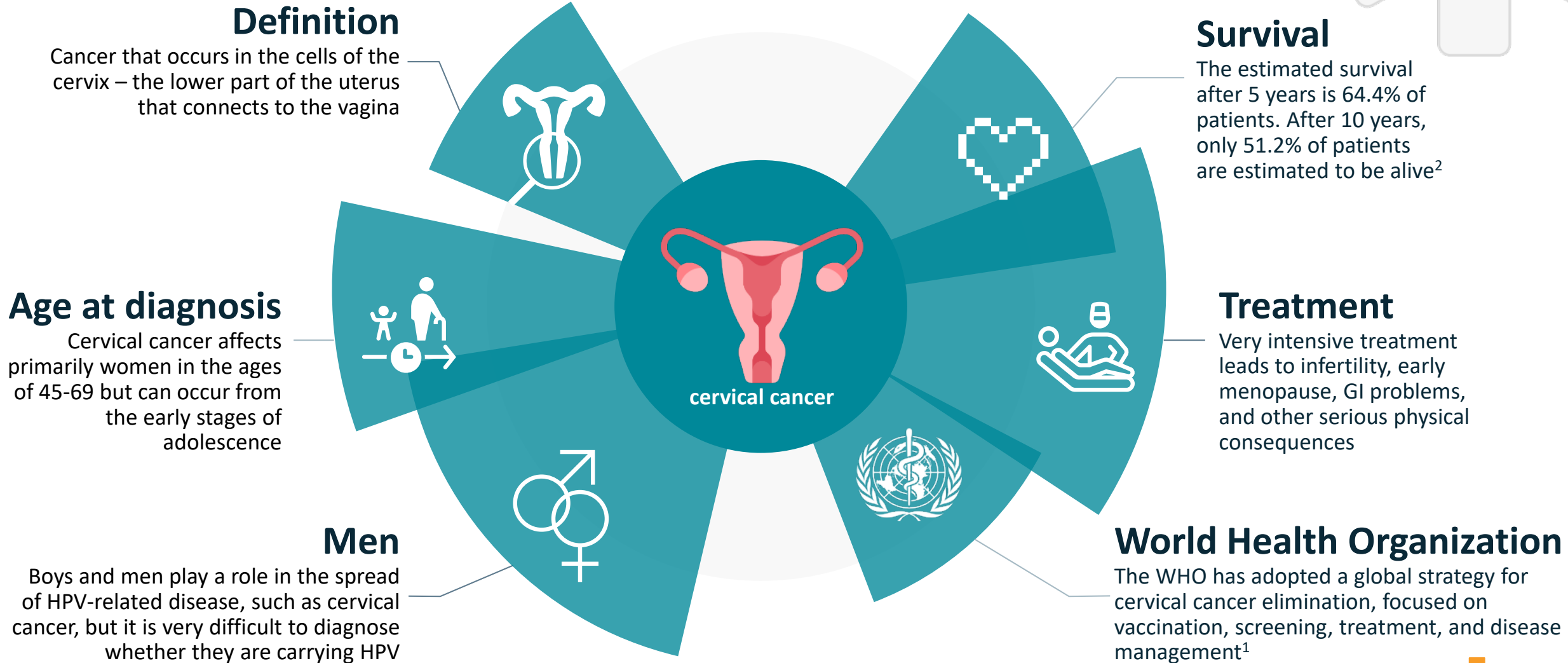
- **Preventable resource use (€)** – Treatment for cervical cancer requires a considerable amount of healthcare resources. On average, a course of treatment for cervical cancer costs over €26,000 (based on an Italian perspective). The total healthcare costs in Italy for the treatment of cervical cancer can be decreased by €74M due to HPV vaccination
- **Preventable resource use (Staff)** – With HPV vaccination, fewer patients require treatment, therefore a total of 493k working hours for nurses can be reallocated

VALUE TO SOCIETY



- **Economic gains** – Vaccinating all women in EU27 against HPV would increase work productivity and labour income by 5.7M working hours and €387.0M respectively
- **Preventable family pain** – Cervical cancer has a significant impact on families and women who want to have children which can be prevented through HPV vaccination

Cervical cancer primarily affects women of working age, who have a 1 in 2 chance of survival after 10 years



1. WHO, 2022.
2. OECD STATLINE (2010-2014)

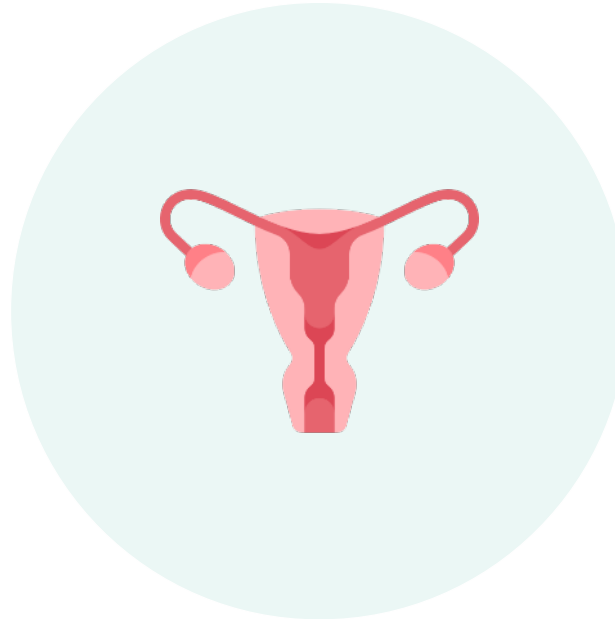
Treatment for cervical cancer includes surgery, chemotherapy, radiotherapy and brachytherapy¹

Surgery

Primary treatment for early stage CC
Radical surgery leads to pain, deformation and sometimes infertility

Radiotherapy

Treatment with curative or palliative intent
Often in combination with other treatment options. Side effects include fatigue, burns and excessive scarring of the radiated tissue



Chemotherapy

Primary treatment for advanced stage CC
Is often given for 6 cycles of 3 weeks during which diarrhoea, nausea, vomiting and infection are common. It can also lead to anaemia, kidney damage, hearing loss and pain.

Brachytherapy

Internal radiation used to increase success of treatment
Very painful for the patient, leading to irritation of the vagina and surrounding tissues. Also leads to fatigue, diarrhoea, nausea, irritation of the bladder, and anaemia.

“At age 27, I was diagnosed with stage IVb cervical cancer. I received chemotherapy, radiotherapy, and brachytherapy. The treatment was very intensive and took a lot out of me physically. The emotional and social consequences have been even more challenging. My life will never be the same again.” -- Patient Expert

Cervical cancer has a major impact on patients, the healthcare system and society

2.5%

of all cancer cases in EU27 is cervical cancer¹

11th

in the EU27 among the most frequently occurring cancers in women¹

12th

in EU27 among the most frequent causes of cancer death¹

Cervical cancer has a major impact on...



Cervical cancer patients

Cervical cancer is a debilitating disease, treatment is intensive, has a prolonged effect on patients' health and wellbeing, and causes a lot of anxiety



The healthcare system

The cost and resource use of cervical cancer treatment are significant

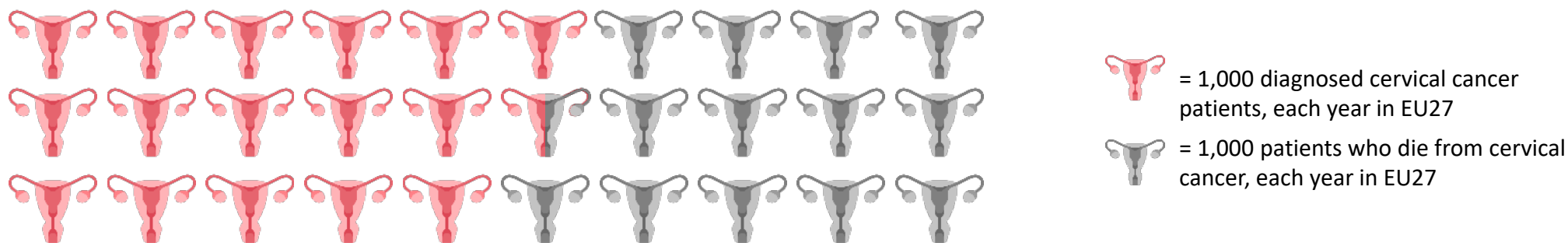


Society as a whole

Cervical cancer patients may not be able to work or care for others, and they may require intensive treatment and care

Current estimates indicate that in EU27, more than 30,000 women are diagnosed with cervical cancer and around 13,500 die from the disease every year¹

Every year, a significant number of women are diagnosed with, or even die from, cervical cancer



There are clear differences between European countries...



Mortality rates are almost threefold higher in Central-Eastern Europe as compared with Western-Europe²



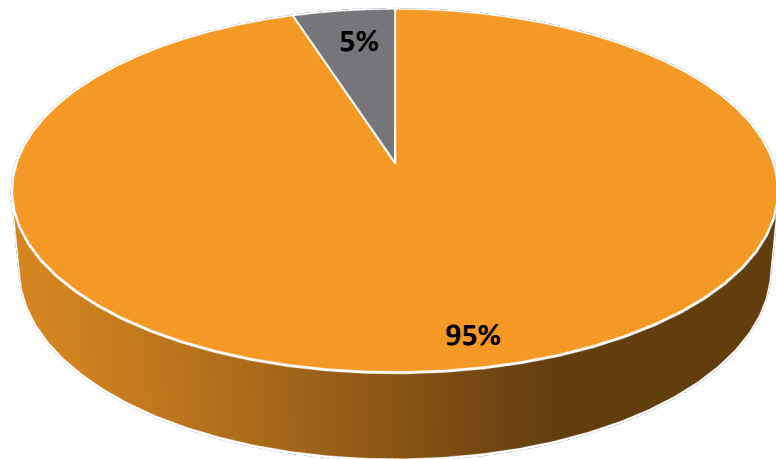
Screening rates vary from over 70% in some EU member states to around 30% in others²



Not all countries cover the **costs** of follow up after a positive screening test or the treatment of precancerous lesions²

Almost all ($\geq 95\%$) cases of cervical cancer are caused by an infection from human papillomavirus (HPV)

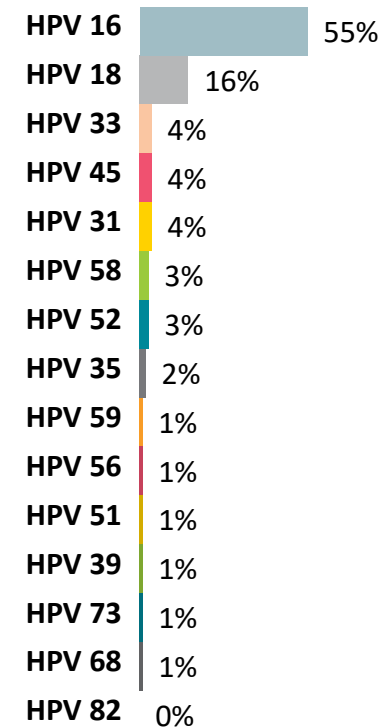
95% of all cervical cancer cases are caused by HPV¹



■ Caused by HPV ■ Other causes

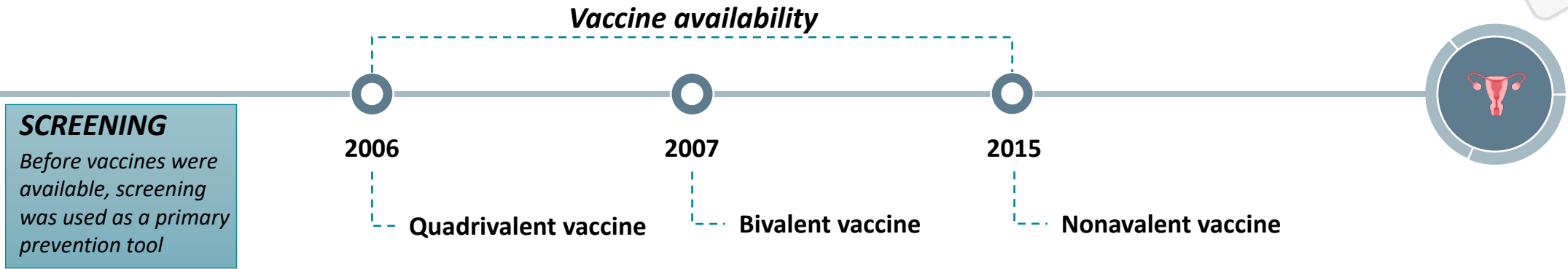
“95%-100% of cervical cancer cases are caused by HPV. There may be a few cases where you cannot find signs of HPV, but this might also be because of the testing methodology.”
-- Oncologist & leading HPV researcher

A large proportion of cervical cancer cases is caused by HPV types 16 and 18²



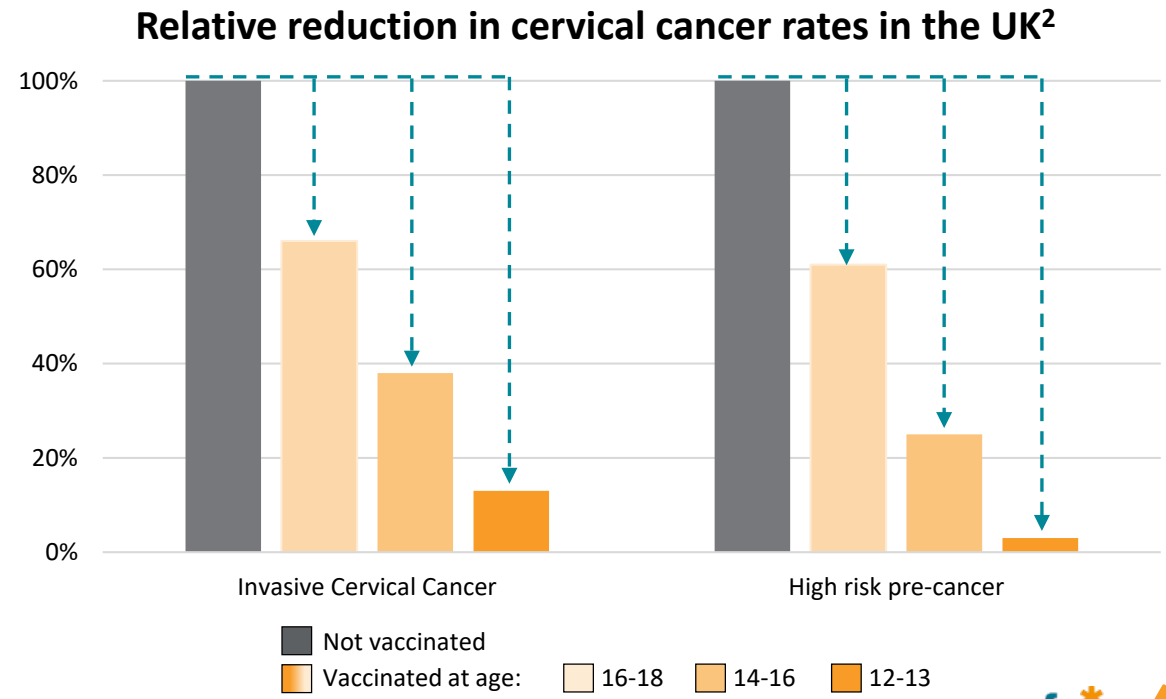
1. FERNANDES, 2022.
2. CUZICK, 2021.

Since 2006, several vaccines against HPV have become available in the EU27, providing the opportunity to prevent most cases of cervical cancer



100% vaccine effectiveness was demonstrated over 12 years in four Nordic countries: no cases of high-grade cervical dysplasia linked to HPV types 16 or 18 were found in a large sample of vaccinated women.¹

“HPV vaccination was a real change of paradigm. It is clearly a story of success: it is very effective, the safety is great, and uptake in lower developed countries is better than it is for screening because eligibility is at a younger age” – Oncologist & leading HPV researcher



1. KJAER, 2020.
2. HPV WORLD, 2022.

In the EU27, every year over 2.2M 12-year-old girls become eligible for HPV vaccination and can benefit from its protection throughout their lives

Eligibility for, and protection by HPV vaccination



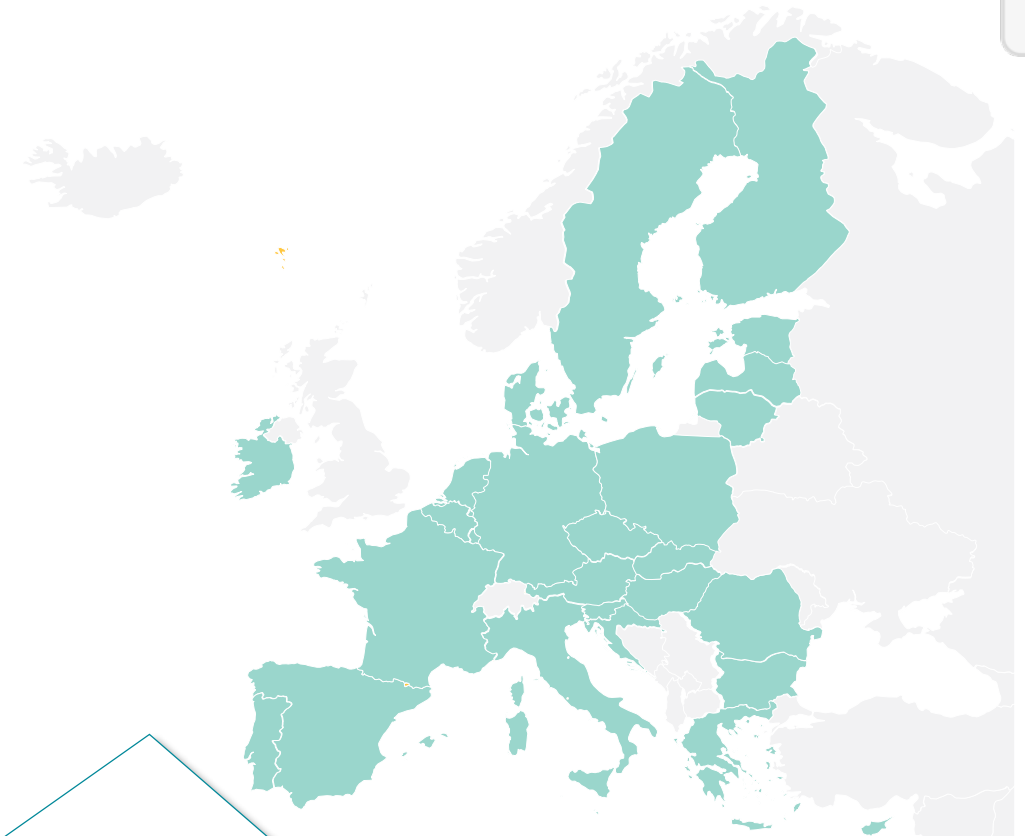
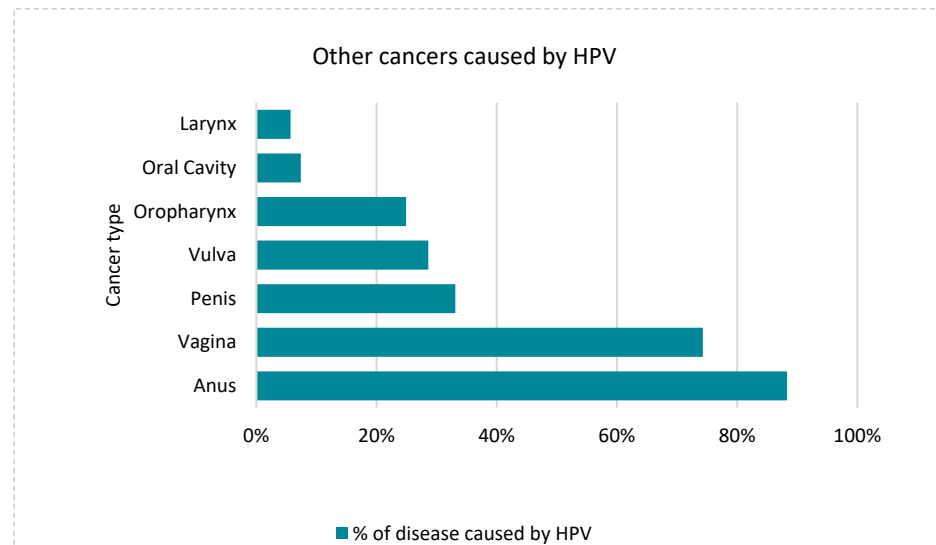
In general, HPV vaccines are available through national vaccination programmes **from 12 years of age**¹



All three vaccines provide great protection, if the required **2 doses** are given.² Vaccination effectiveness is at least 94.7%³



The vaccines also offer “cross”-protection for other HPV-related disease such as genital warts and other types of cancer⁴



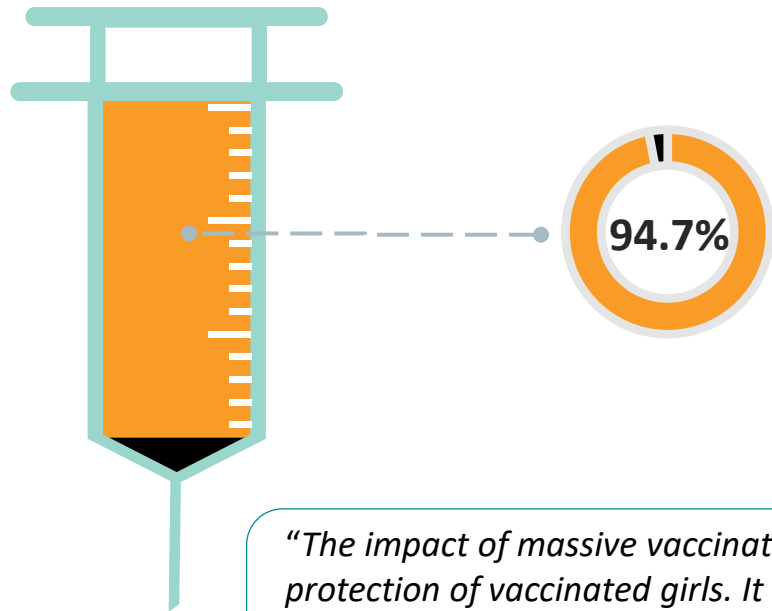
“HPV vaccination provides cross-protection for other diseases as well. This effect is not negligible, especially when it comes to genital warts.”

-- Oncologist & leading HPV researcher

1. BONNANI, 2020.
2. MISHRA, 2015.
3. KJAER, 2020.
4. DE SANJOSÉ, 2016.

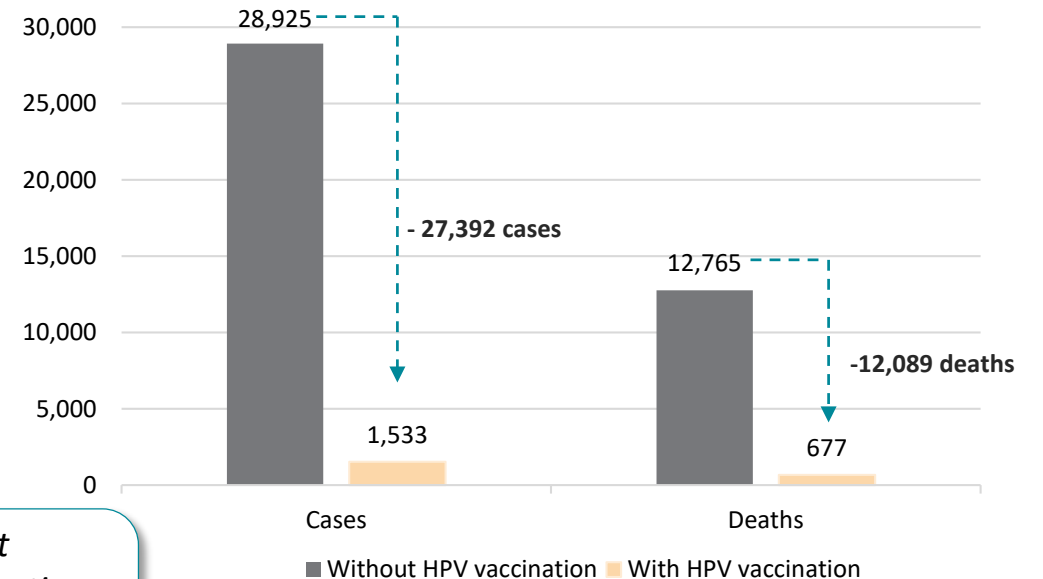
More than 27,000 cervical cancer cases and 12,000 deaths can be prevented by HPV vaccination, each year

HPV vaccines are at least 94.7% effective in preventing HPV infections¹



“The impact of massive vaccination is larger than the direct protection of vaccinated girls. It reduces the risk of HPV infection per sexual contact. So we achieve protection of the non-vaccinated as well.” – Oncologist & leading HPV researcher

This means that, every year, over 27,000 cases and 12,000 cervical cancer-related deaths can be prevented by HPV vaccines



1. KJAER, 2020.
2. FERNANDES, 2020.

The burden of cervical cancer screening can be reduced by 57% with HPV vaccination, as vaccinated women require less screening

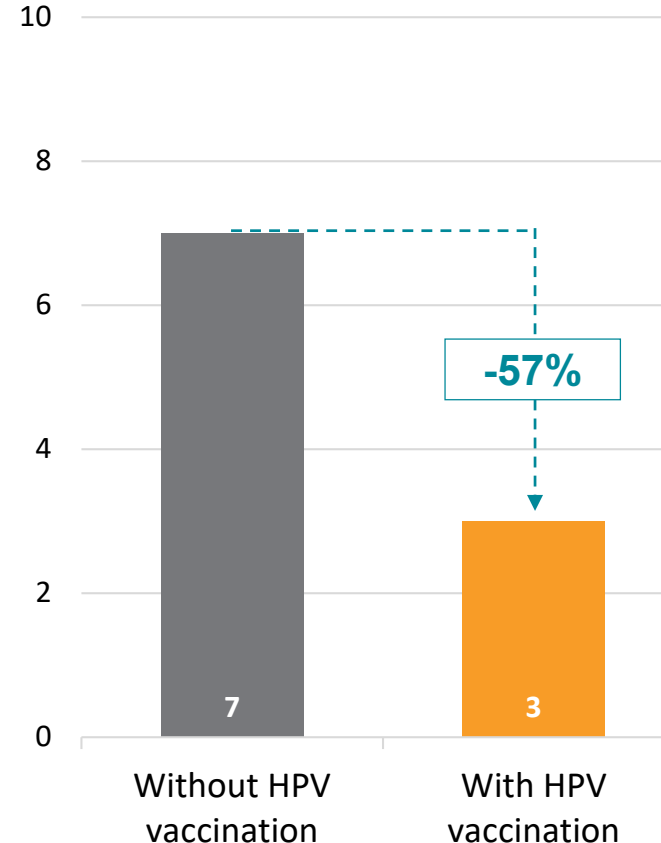
The burden of cervical cancer screening is high

- Each year, 19.3 M women require cervical cancer screening in the EU27
- After each screening, women wait on average 2-6 weeks for the results
- Screening and testing for cervical cancer can cause a lot of stress, as screening is uncomfortable and is associated with long waiting times for the results

“After being cured from cervical cancer, every check up is very stressful. The waiting time between the examination and the results is nerve-racking” -- Patient Expert

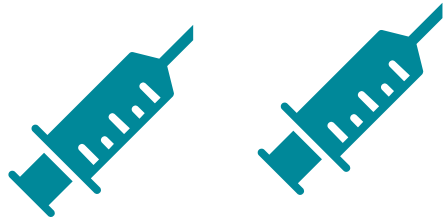
HPV vaccination significantly decreases the burden of cervical cancer screening¹

Number of lifetime cervical cancer screenings with and without HPV vaccination



“The generalized use of vaccines may have a counterbalance in reducing the needs for screening. Vaccinated women have to come in for screening much less, and the funds could be moved to vaccination.”
-- Oncologist & leading HPV researcher

Treatment for cervical cancer requires a considerable amount of healthcare resources



The total cost¹ for two courses of vaccination are estimated at

€132.71



Unvaccinated women need 7 screens during their lifetime. Pap smear cost¹ is estimated at

€18.05



The cost of treatment² is country dependent, and could increase over the next decade

>€20,000

 *Deep dive into Italy* 

1. HAEUSSLER, 2015.
2. MENNINI, 2017.

On average, a course of treatment for cervical cancer costs over €26,000 (based on an Italian perspective)

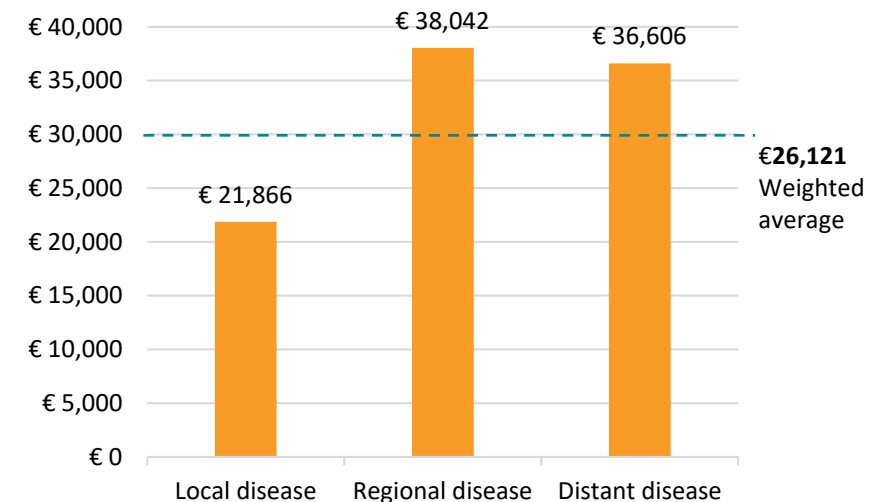
Per-patient cervical cancer treatment costs are significant

Deep dive into Italy

Based on an Italian cost estimate, cervical cancer treatment costs are:

- **Locally spread disease**
Costs for treating locally spread cervical cancer are €21,866 on average¹
- **Regionally spread disease**
Costs for treating cervical cancer which has spread to the surrounding tissue are €38,042 on average¹
- **Distant disease**
Costs for treating metastasized cervical cancer are €36,606 on average¹

Average (weighted) costs per patient are €26,121^{1,2}



A €74M decrease in the total healthcare costs for the treatment of cervical cancer in Italy can be achieved through HPV vaccination

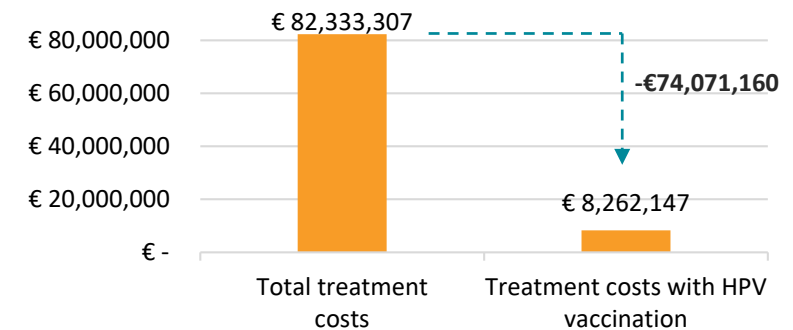
A significant amount of costs spent on cervical cancer treatments can be prevented through HPV vaccination

Deep dive into Italy

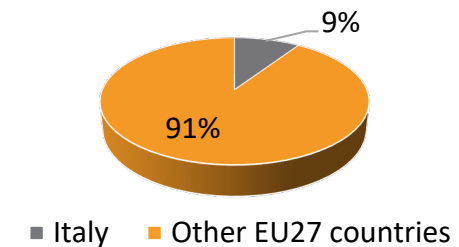
- The average (weighted) cost per patient in Italy is €26,121
- The number of potentially prevented cervical cancer cases due to HPV vaccination is 2,836
- This means that ~€74M spent on cervical cancer treatment can be prevented by HPV vaccination
- Italy has only 9% of the potentially prevented cervical cancer cases in EU27



Cervical cancer treatment costs in Italy



Potentially prevented cervical cancer cases



With HPV vaccination, a total of 493k working hours for nurses can be reallocated in the healthcare system, as fewer patients require treatment

Cervical cancer treatment is labour intensive

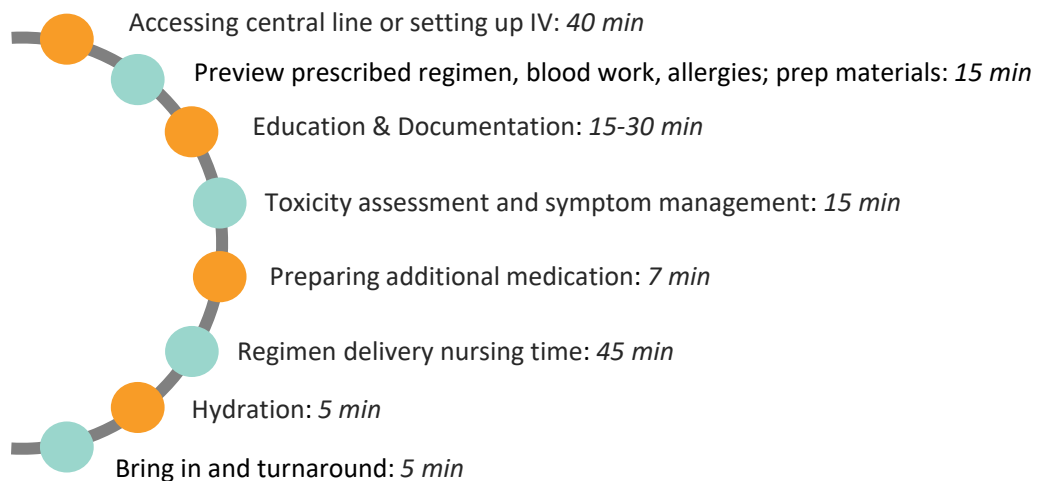


Chemotherapy – Patients require 6 courses, each taking a nurse ~2 hours to complete. This equates to 12 hours per patient¹



Radiotherapy – Patients require at least 24 sessions, each taking a nurse ~15 minutes to complete. This equates to 6 hours per patient²

Nurse time break-down for course of Chemotherapy¹



HPV vaccination could save many nurse hours spent on cervical cancer treatment

Assuming that all cervical cancer patients require chemotherapy and radiotherapy; preventing the cancer by vaccinating all women in EU27 against HPV would save:

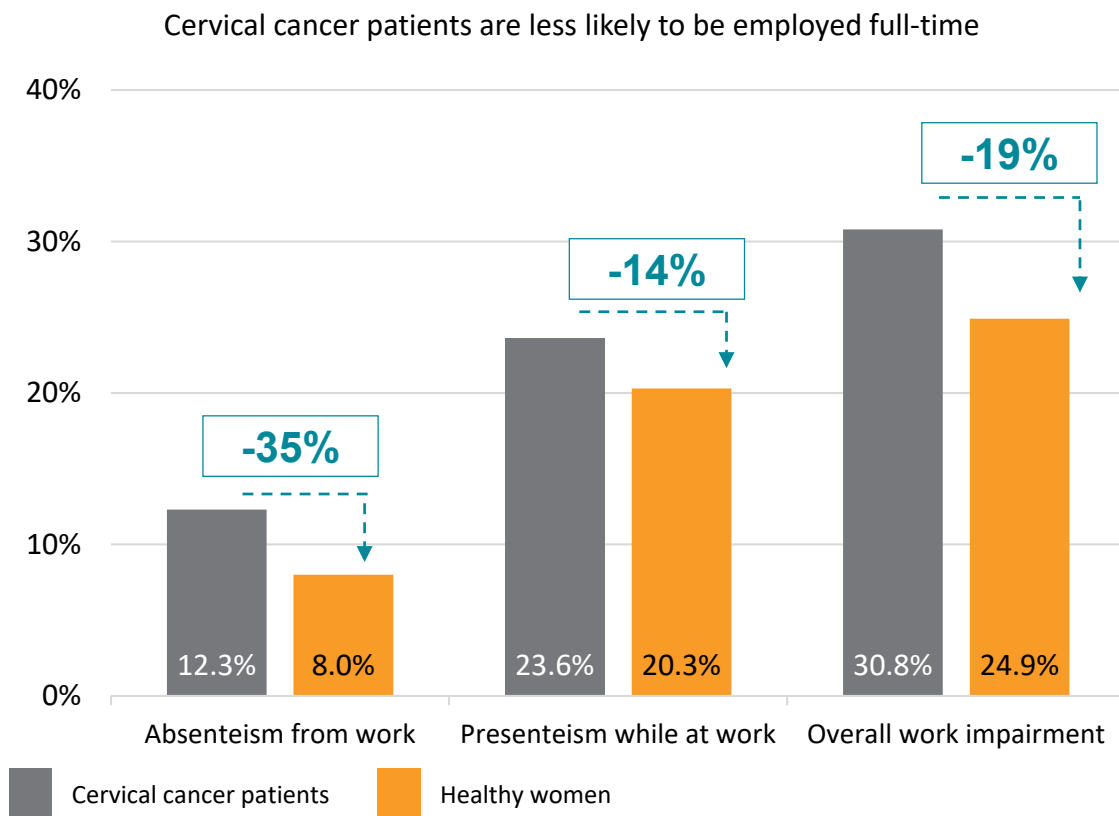


493,050 nurse working hours per annum

“In addition to savings on treatment, we can also save on screening costs. There was a full industry around screening, this was a gigantic piece of work that involved a high cost.” – Oncologist & leading HPV researcher

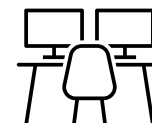
Vaccinating all eligible women in EU27 against HPV would increase work productivity and labour income by 5.7M working hours and €386M, respectively

Cervical cancer patients are less likely to be full-time employed and are more impaired at work, resulting in productivity loss¹

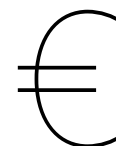


Preventing cervical cancer through HPV vaccination results in significant economic benefits²

Preventing cervical cancers by vaccinating all women in EU27 against HPV would increase:



Annual productivity in EU27 by **5.6M working hours**



Annual labour income in EU27 **€386M**

"I lost my job because I had a chemo brain, making it impossible to focus. I had very low energy levels and my work capacity was severely affected. I was unable to function professionally" -- Patient Expert

1. DOANE, 2019.
2. EUROSTAT, 2022.

Cervical cancer has a significant impact on families and women who want to have children – this can be prevented through HPV vaccination

Cervical cancer burden for families¹



On average in the EU27, each year:

3,039 mothers with children (≤ 18 years old) living at home die of cervical cancer

5,167 children living at home (≤ 18 years old) lose their mother due to cervical cancer

Cervical cancer burden for adolescent women



Burden of cervical cancer persists after treatment:

- Unfortunately, after most treatment for cervical cancer, women will not be able to get pregnant
- This can result in stress and psychosocial burden for women surviving cervical cancer

"I had to accept that my life will be completely different than what I had always envisioned. I will never be who I was before. I entered menopause at the age of 27 and will not be able to conceive a child" -- Patient Expert

Looking towards the future...



Education

People have the right to make an informed decision about HPV vaccination, so education is key

Expanding the use of vaccination

Globally, In 2006–2017, 100 million adolescent girls received at ≤ 1 dose of the HPV vaccine – 95% were in high income countries

Gender-neutral vaccination

26 countries in the European region are currently, or will be, including boys in their vaccination programmes

HPV diagnosis in men

HPV-related disease is well studied in women, but until recently the natural history of HPV among males was relatively unknown

Improved access and new treatment options for cervical cancer patients

Currently the five-year survival rate for early-stage cancer is more than 80% in countries where timely diagnosis and high-quality treatment are available

Assumptions for Cervical Cancer case study



Parameter	Value	Rationale
Proportion of cervical cancer cases caused by HPV	95%	Conservative assumption based on multiple sources
Estimated effectiveness of vaccine	94.7%	Kjaer et al. (2020) estimate 100% effectiveness with a lower 95%-confidence interval of 94.7%
Age of vaccination eligibility	12 years	Seems to be a good assumption looking at the spread between countries in EU27 (more information in calculations file)
Target vaccination coverage	90%	European Cancer Organisation (2020) & WHO target
Current number of lifetime screens advised	7 screens	Every 5 years from age 35 to age 65. Based on the European guidelines for quality assurance in cervical cancer screening. This is dependent on policy per country, but most countries are relatively close to this; some start earlier or have more frequent screens, which makes this a conservative assumption.
Lifetime screens required after vaccination	3	Landy et al. (2018) estimate that HPV16/18-vaccinated women require three lifetime screens, HPV16/18/31/33/45/52/58-vaccinated women require two lifetime screens
Cervical cancer stage at diagnosis	Local disease: 72.6% Regional disease: 14.9% Distant disease: 12.5%	Landy et al. (2016)
Reduction in workload for cervical cancer patients	19%	Conservative assumption based on interviews
Scope	EU27 countries	EU27 includes Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovenia, Slovakia, Spain, Sweden.

Reference list

Research articles

- Baker P, Kelly D, Medeiros R (2020). Viral Protection: Achieving the Possible. A Four Step Plan for Eliminating HPV Cancers in Europe. European Cancer Organisation; Brussels.
- J Cuzick, R Adcock, CM Wheeler (November 2021). HPV genotype-specific risk for cervical cancer. www.HPVWorld.com, 181
- Fernandes A, Viveros-Carreño D, Hoegl J, et al. Human papillomavirus-independent cervical cancer. *International Journal of Gynecologic Cancer* 2022; **32**:1-7.
- Haeussler K, Marcellusi A, Mennini FS, Favato G, Picardo M, Garganese G, Bononi M, Costa S, Scambia G, Zweifel P, Capone A, Baio G. Cost-Effectiveness Analysis of Universal Human Papillomavirus Vaccination Using a Dynamic Bayesian Methodology: The BEST II Study. *Value Health* 2015; **18**(8):956-68. doi: 10.1016/j.jval.2015.08.010. Epub 2015 Oct 21. PMID: 26686779.
- Kjaer SK, Nygård M, Sundström K, et al. Final analysis of a 14-year long-term follow-up study of the effectiveness and immunogenicity of the quadrivalent human papillomavirus vaccine in women from four nordic countries. *EClinicalMedicine* 2020; **23**:100401.
- Mishra GA, Pimple SA, Shastri SS. HPV vaccine: One, two, or three doses for cervical cancer prevention? *Indian J Med Paediatr Oncol* 2015; **36**(4):201-206.
- De Sanjosé S, Serrano B, Tous S, Alejo M, Lloveras B, Quirós B, Clavero O, Vidal A, Ferrándiz-Pulido C, Pavón MÁ, Holzinger D, Halc G, Tommasino M, Quint W, Pawlita M, Muñoz N, Bosch FX, Alemany L; RIS HPV TT, VVAP and Head and Neck study groups. Burden of Human Papillomavirus (HPV)-Related Cancers Attributable to HPVs 6/11/16/18/31/33/45/52 and 58. *JNCI Cancer Spectr* 2019; **2**(4):pky045.
- Landy R, Pesola F, Castañón A, Sasieni P. Impact of cervical screening on cervical cancer mortality: estimation using stage-specific results from a nested case-control study. *Br J Cancer* 2016; **115**(9):1140-1146.
- Mennini FS, Bonanni P, Bianci F, de Waure C, Baio G, Plazzotta G, Uhart M, Rinaldi A, Largeron N. Cost-effectiveness analysis of the nine-valent HPV vaccine in Italy. *Cost Eff Resour Alloc* 2017; **15**:11.
- Doane MJ & Nwankwo C. Economic and humanistic burden associated with cervical cancer: An analysis of patient-reported outcomes in Europe (the H-EMBRACE study). *Gynecologic Oncology* 2019; **154**(1):167-168. ISSN 0090-8258, <https://doi.org/10.1016/j.ygyno.2019.04.392>.
- Landy R, Windridge P, Gillman MS, Sasieni PD. What cervical screening is appropriate for women who have been vaccinated against high-risk HPV? A simulation study. *Int J Cancer* 2018; **142**(4):709-718.
- Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, Clarke-Pearson DL, Insalaco S. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999; **340**(15):1144-53. Erratum in: *N Engl J Med* 1999; **341**(9):708.
- Green E, Preyra C, Stewart J, McLennan C, Bland R, Dus T, Langhorn M, Beattie K, Cheung A, Hertz S, Sechter H, Burns J, Angus H, Sawka C. Determining resource intensity weights in ambulatory chemotherapy related to nursing workload. *Can Oncol Nurs J* 2012; **22**(2):114-128.

Websites

- World Health Organization. Cervical Cancer Elimination Initiative. <https://www.who.int/initiatives/cervical-cancer-elimination-initiative> Accessed July 2022.
- OECD Stats. Health Care quality Indicators: Cancer Care <https://stats.oecd.org/Index.aspx?QueryId=51882#> . Accessed May 2022.
- <https://appsso.eurostat.ec.europa.eu/nui/show.do> Accessed May 2022.
- HPV World. The impact of HPV vaccination program on CIN3 and cervical cancer incidence in England. <https://www.hpvworld.com/articles/the-impact-of-hpv-vaccination-program-on-cin3-and-cervical-cancer-incidence-in-england/> Accessed Aug 2022.
- Eurostat. https://ec.europa.eu/eurostat/databrowser/view/DEMO_PJAN_custom_3018463/default/table?lang=en Accessed July 2022.
- European guidelines for quality assurance in cervical cancer screening. <https://op.europa.eu/en/publication-detail/-/publication/a41a4c40-0626-4556-af5b-2619dd1d5ddc> Accessed July 2022.
- Eurostat Euroindicators. March 2022. Euro area unemployment at 6.8% <https://ec.europa.eu/eurostat/documents/2995521/14613608/3-03052022-AP-EN.pdf/36631a07-778c-efb0-01f2-8a052bde985e?t=1651561306689#:~:text=In%20March%202022%2C%20the%20euro,from%207.5%25%20in%20March%202021> Accessed May 2022.
- <http://appsso.eurostat.ec.europa.eu/nui/submitViewTableAction.do> Accessed July 2022.
- Eurostat. https://ec.europa.eu/eurostat/databrowser/view/EARN_SES_HOURLY_custom_3018915/default/table?lang=en Accessed July 2022.
- Eurostat. https://ec.europa.eu/eurostat/databrowser/view/EARN_SES_ANNUAL_custom_3021783/default/table?lang=en Accessed July 2022.
- HPV World. HPV infection and diseases among men. <https://www.hpvworld.com/articles/hpv-infection-and-diseases-among-men-results-from-the-hpv-infection-in-men-him-study/> Accessed August 2022.

Reports

- Joint Research Centre & European Network of Cancer Registries – Cervical cancer factsheet in 2020 for EU-27 countries. 3 Jan 2022. Available at: <https://ecis.jrc.ec.europa.eu/factsheets.php>
- Human Papillomavirus and Related Cancers, Fact Sheet 2021. ICO/IARC Information Centre on HPV and Cancer. 22 Oct 2021. Available at: https://hpvcentre.net/statistics/reports/ITA_FS.pdf
- World Health Organization (WHO). Global strategy to accelerate the elimination of cervical cancer as a public health problem. November 2020. ISBN: 9789240014107.

Interviews

Interviews conducted in July and August 2022 with 1 Patient Expert and 1 Healthcare Professionals (KOLs).

Allowing Rheumatoid Arthritis patients to live a normal life with biologics



CASE OUTLINE

- I. **Case for change**
 - *Situation*
 - *Challenge*
 - *Paradigm shift*
 - *Patient population*
- II. **Value to patients**
- III. **Value to the healthcare system**
- IV. **Value to society**
- V. **Annex**
 - *Key assumptions*
 - *Reference list*

Case summary | Rheumatoid Arthritis

Allowing RA patients to live a normal life with biologics

CASE FOR CHANGE



- **Situation** – Rheumatoid Arthritis (RA) is a chronic, destructive autoimmune disease for which 32% of patients did not have access to effective treatments before 1998
- **Challenge** – Standard of care (SoC) treatment is conventional disease modifying antirheumatic drugs (cDMARDs), most often starting with methotrexate. These treatments work insufficiently for 32% of patients who remain in need for a better working treatment
- **Paradigm shift** – In 1998, the first biological DMARD (bDMARD) entered the market, providing these patients with a new treatment option
- **Population** – The prevalence of Rheumatoid Arthritis is 0.5%–1.0%, meaning there are 2,236,037–4,472,075 patients with RA in EU27 in 2021

VALUE FOR PATIENTS



- **Reduced RA symptoms** – Biological DMARDs are effective in improving disease activity which leads to symptom reduction: less pain, less joint damage, and better overall health
- **Radical change of patient experience** – bDMARDs are significantly more effective at reducing DAS28 to <2.6 compared with cDMARDs, drastically improving patient experience
- **Slowed disease progression** – Treatment with bDMARDs does not only lead to symptom reduction but also better disease control, showing less progression of joint damage
- **Improved Quality of Life** – Patients are more mobile and less affected by the symptoms of their disease, causing an improved Quality of Life (QoL)

VALUE TO THE HEALTHCARE SYSTEM



- **Preventable resource use** – More effective disease management due to bDMARD treatment, as well as reduction in resource utilisation.

VALUE TO SOCIETY



- **Economic gains** – bDMARD use results in reduced absenteeism and presenteeism in EU27 RA patients, resulting in increased productivity
- **Enjoying life again** – Because patients are less troubled by their disease, they can enjoy time with their family and friends again

TOWARDS THE FUTURE



- The innovation that bDMARDs have brought to RA patients is life changing, but there remain unmet needs in this therapy area

Rheumatoid Arthritis is a chronic, destructive autoimmune disease for which 32% of patients did not have access to effective treatments until 1998



Rheumatoid Arthritis



Rheumatoid Arthritis (RA) is a chronic, destructive **autoimmune** disease that causes **inflammation** of the **joints and other systemic issues**¹



RA can develop at all ages, but is mostly diagnosed between 30 and 60 years of age, and is twice as common in women as in men¹



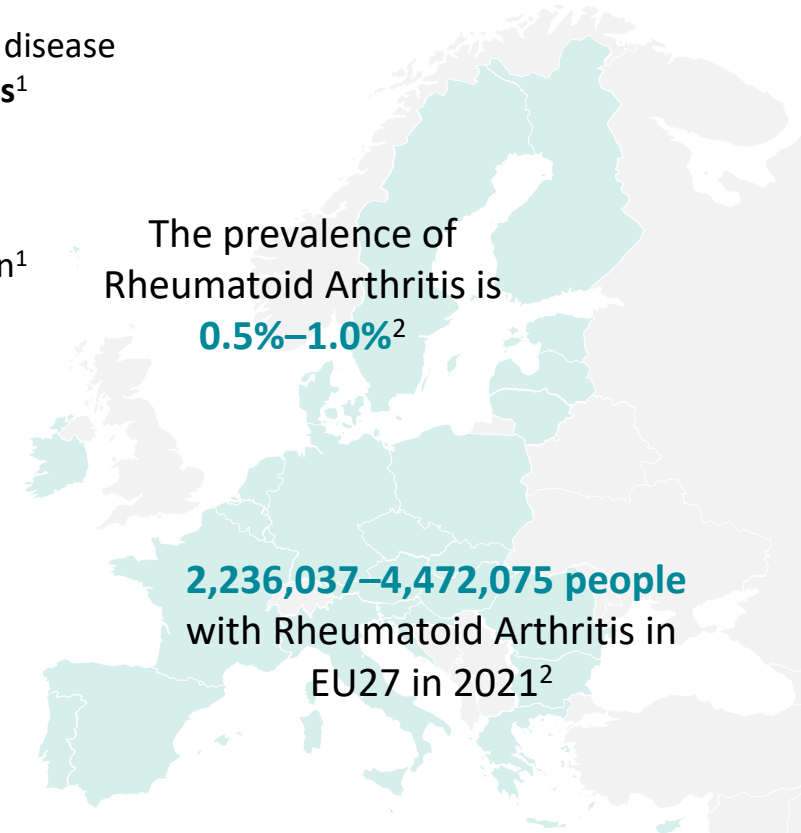
Standard of care (SoC) treatment is conventional disease modifying antirheumatic drugs (cDMARDs), most often starting with methotrexate³



These treatments **work insufficiently for 32% of patients**, who remain in need for a better working treatment³



In 1998 the first **biological DMARD** (bDMARD) entered the market, providing these patients with a **new treatment option**³



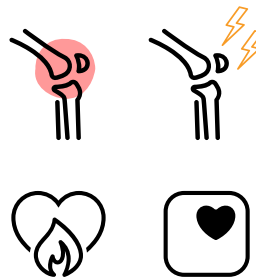
1. HEALTHLINE, ACCESSED JULY '22
2. MINICHELLO, ET AL. 2016
3. KALÓ, ET AL. 2017

Biological DMARDs are effective in improving disease activity, leading to symptom reduction: less pain, less joint damage, and better overall health

Inflammatory activity cannot be measured using one single variable. The Disease Activity Score (DAS) was developed to measure disease activity¹

DAS28 score is calculated on the basis of:²

- Number of swollen joints (out of the 28)
- Number of tender joints (out of the 28)
- Inflammation values in the blood (C reactive protein (CRP) or erythrocyte sedimentation rate (ESR))
- Answers to a patient health assessment questionnaire



DAS28 score 0–9.4	Translation into disease activity ²
<2.6	Disease remission
2.6–3.2	Low disease activity
3.2–5.1	Moderate disease activity
>5.1	High disease activity

Many studies have investigated the efficacy of bDMARDs³



Different treatment groups

- bDMARD monotherapy vs. cDMARDs +/- placebo
- bDMARDs + cDMARDs vs. cDMARDs +/- placebo



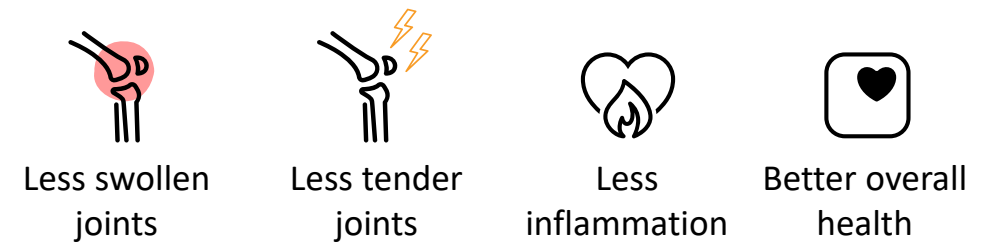
Different patient populations

- Treatment naïve patients
- Patients previously treated with cDMARDs



These studies prove that a bigger % of patients on bDMARDs scored <2.6 or 2.6–3.2 on DAS28 than patients on cDMARDs³

...meaning:

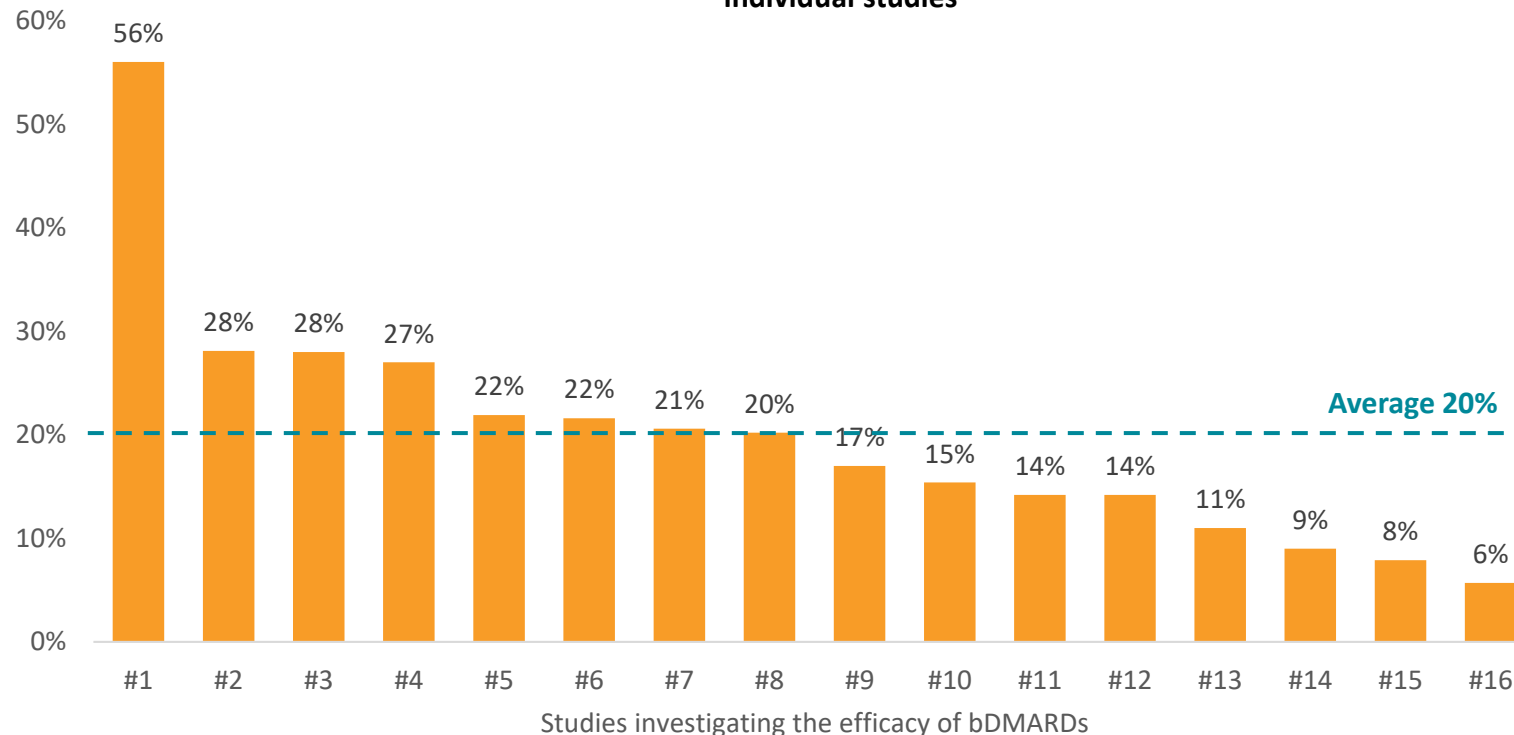


1. VAN RIEL & RENSKERS 2016
 2. ARTHRITIS HEALTH, ACCESSED JULY '22
 3. NICE TECHNOLOGY ASSESSMENT REPORT TA375 P.101-102

bDMARDS are significantly more effective at reducing DAS28 to <2.6 compared with cDMARDS, drastically improving patient experience



Absolute improvement of patients scoring DAS28 score <2.6 for patients using bDMARDS vs cDMARDS across 15 individual studies



Treatment with bDMARDS changes the patient's experience of their disease²

- "After the treatment, I feel like I can do things that everyone else can do"
- "I was mostly just thankful to get back to being self-sufficient"
- "I didn't want him to remember me as the mum who was always in pain and crying. And I'm not that mum anymore"
- "It's significant when you do something that's very normal, and you realize five minutes into it that you're able to do it"
- "Before my current medication, I would have been happy selling the business and living a lifestyle where I didn't have to do much. But now, I want to do better in business and life."

Patients receiving bDMARDs instead of cDMARDs are experiencing fewer RA symptoms, drastically improving patient experience



Disease activity of patients is scored after treatment

DAS28 score	<2.6	2.6–3.2	3.2–5.1	>5.1
Disease activity	Remission	Low	Moderate	High

+20%
more patients in
the bDMARDs
treatment group
vs. cDMARDs
treatment group¹

Disease remission: signs and symptoms are relieved for an extended period of time³

Treatment with bDMARDs changes the patient's experience of their disease²

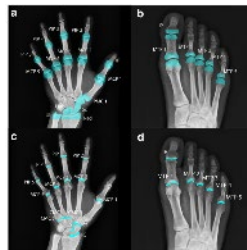
- "After the treatment, I feel like I can do things that everyone else can do"
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- "I didn't want him to remember me as the mum who was always in pain and crying. And I'm not that mum anymore"
- "It's significant when you do something that's very normal, and you realize five minutes into it that you're able to do it"
- "Before my current medication, I would have been happy selling the business and living a lifestyle where I didn't have to do much. But now, I want to do better in business and life."

Treatment with bDMARDs does not only lead to symptom reduction but also greater disease control and less progression of joint damage

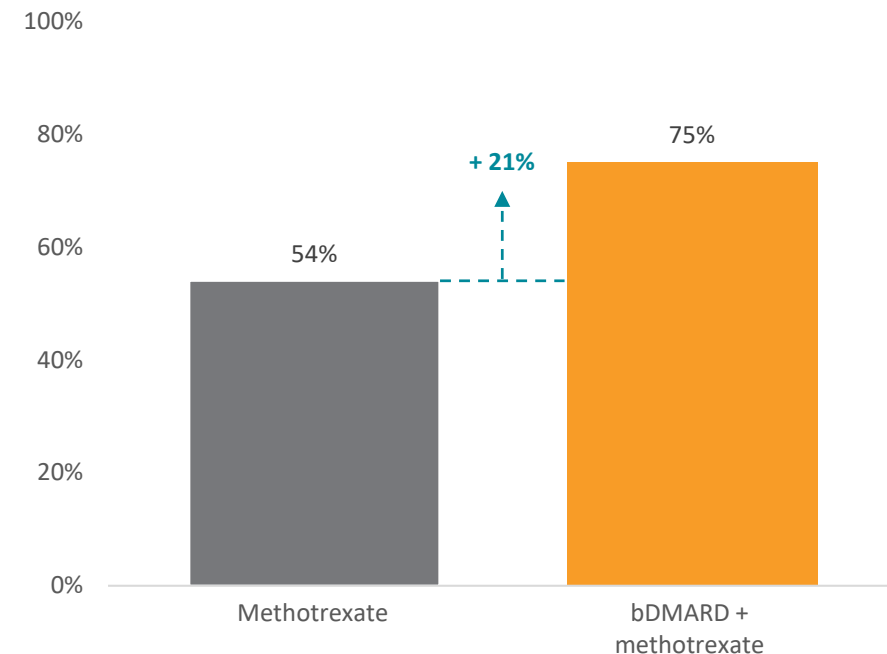
75% of patient showed no signs of disease progression and joint damage 1 year after treatment initiation with bDMARDs¹

+21% compared with the proportion of patients showing no disease progression 1 year after treatment initiation with methotrexate¹

Structural changes of bone and cartilage are the hallmarks of rheumatoid arthritis. Disease progression is measured by scoring joint erosion and joint space narrowing in radiographs of hands and feet^{2,3}



Proportion of patients with radiographic non-progression 52 weeks after start of treatment (%)¹



Patients taking bDMARDs are more mobile and less affected by the symptoms of their disease, causing an improved Quality of Life (QoL)

+44% improvement in quality of life is experienced by female patients one year after switching their treatment to bDMARDs¹

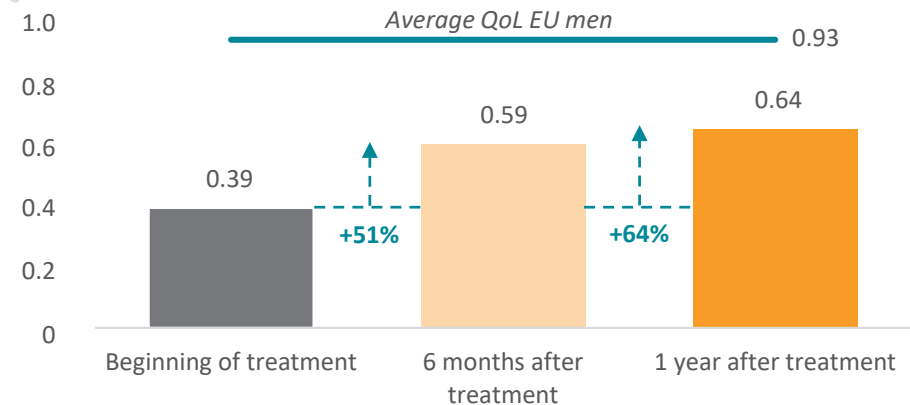
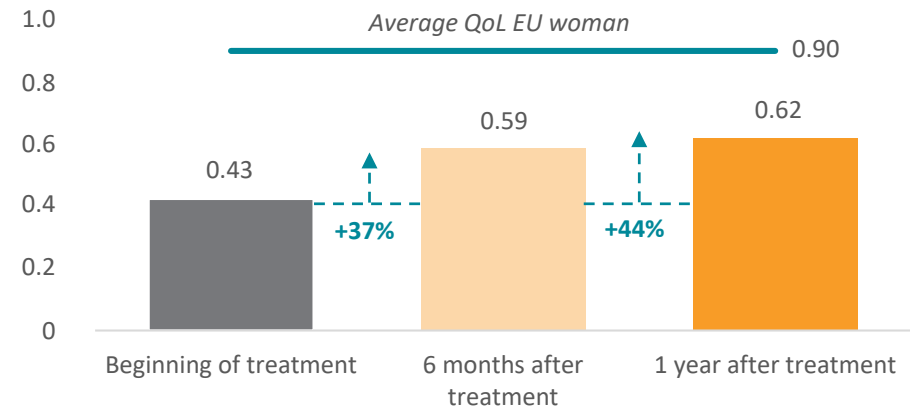
+64% improvement in quality of life is experienced by male patients one year after switching their treatment to bDMARDs¹

"It is revolutionary what biologics brought to patients"
– Patient Expert

Quality of Life (QoL) can be measured with various instruments, of which EQ5D is globally accepted. EQ5D calculates a score ranging from 0 to 1²



Improvement in QoL* with treatment switch to bDMARDs¹



*MEASURED BY EQ5D
1. BOYADZIEVA, ET AL. 2018
2. EUROQOL, ACCESSED AUGUST '22

Because patients are less troubled by their disease, they feel self-sufficient and can enjoy time with their family and friends again



70-80% more time able to perform household work

Treatment with bDMARDs gives patients their life back

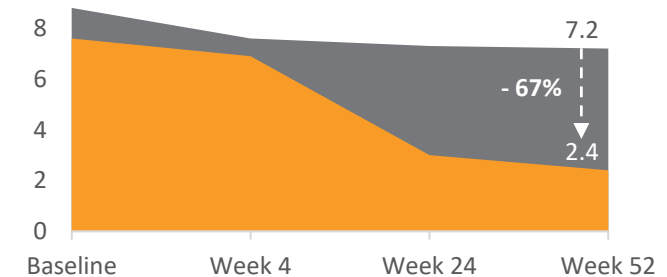


40-60% more time able to spend with family and friends

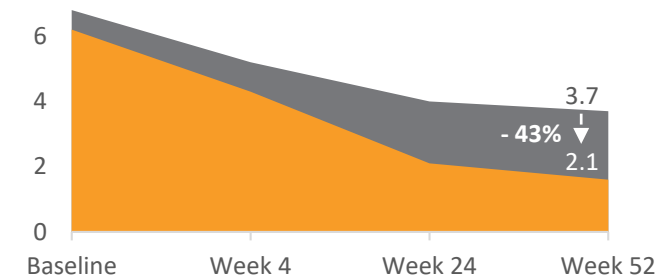
“People were stuck at home, feeling depressed because people are human beings and should be able to socialize. Now you can contribute again to your family, to the society, travel and see your friends again”

– Patient Expert

Lost days of household work per month¹



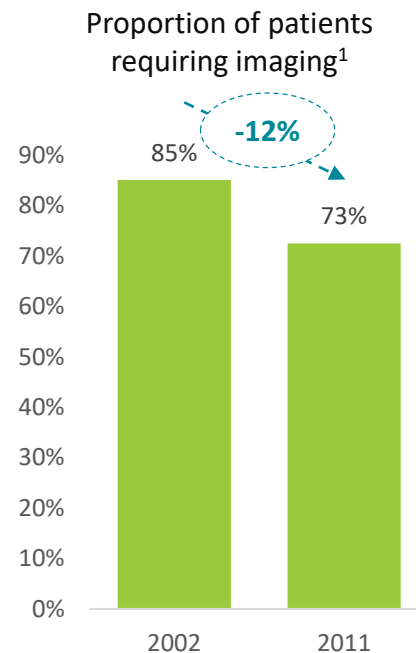
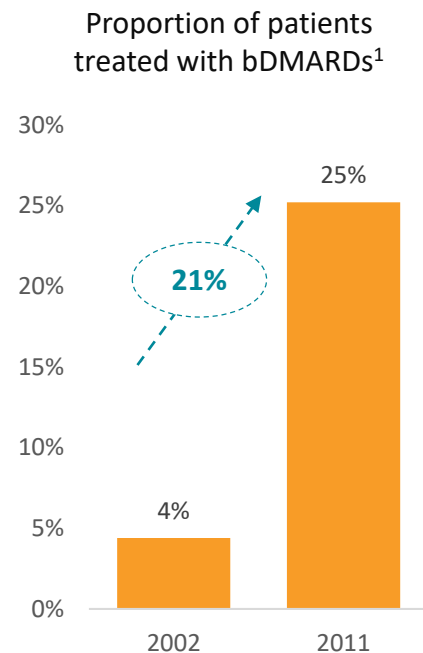
Lost days of family, social, and leisure activity per month¹



Treatment Placebo + methotrexate bDMARDs + methotrexate

bDMARD treatment leads not only to more effective disease management, but to a reduction in resource utilisation as well

 Analysis of National Database of the German Collaborative Arthritis Centres from 2002 to 2011



"I always tell my students that in the past my waiting room was full of wheelchairs. Now we only see patients in a wheelchair when they had a normal accident because they can live a normal life again"
– Healthcare Professional



"We used to have a special clinic for the care of Rheumatoid Arthritis patients who had severe pain and serious damage to their joints. This clinic closed in 1997 because we can help patients much better"
– Healthcare Professional²

bDMARD use results in reduced absenteeism and presenteeism in EU27 RA patients, resulting in increased productivity

132M workdays

gained per year for the entire RA population (absenteeism)

+87M workdays

gained with full productivity per year for the entire RA population (presenteeism)

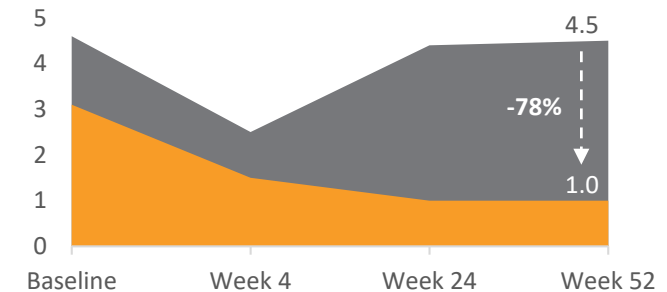
“bDMARDs provided patients with the ability to keep their normal life. Work life but also personal life... First, they had lower productivity but now they can contribute and maintain jobs”

– Healthcare Professional

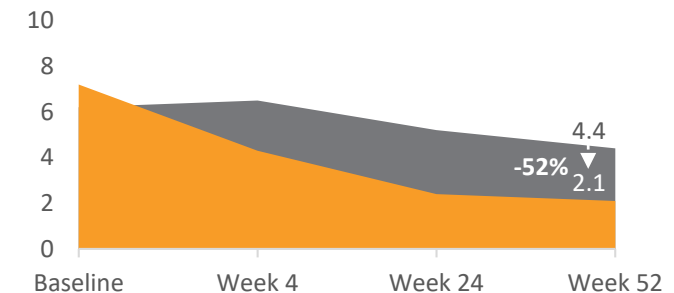
“You feel useful again”

– Patient Expert

Workdays missed per month (absenteeism)¹



Workdays with reduced productivity by ≥50% per month (presenteeism)¹



Treatment Placebo + methotrexate bDMARDs + methotrexate

The innovation that bDMARDs brought to RA patients is life changing, but there are remaining unmet needs in this patient population

bDMARDs bring great benefits to RA patients and allow them to participate in life again.

However, these patients are still chronic patients and there **are remaining unmet needs**



Early diagnosis

“My dream for the future is that we have no disability caused by rheumatoid disease anymore. To reach that, we should raise awareness so that people have the right diagnosis and treatment as soon as possible.”

– Patient Expert

“People should recognize when they should visit the doctors with their symptoms and the GP should recognize when to refer the patient to the rheumatologist.”

– Patient Expert

“All stakeholders should collaborate to ensure that patients are identified as early as possible: patients, doctors, specialists.”

– Patient Expert



New targets for treatment & diagnoses

“There are 3 types of patients: patients doing very well, patients doing very badly, and the rest of patients. For the first group, we don’t have an unmet need. For the second group, we need new treatments. This can be new therapies for targets currently in clinical development or new combination between bDMARDs and add-on safe therapies. For the last group, we will not change their treatment because they are responding but there is room for improvement. This can be done by having a holistic treatment approach, including physical activity, psychotherapy and diet counselling.”

– Healthcare Professional



Cure or prevention

“Currently patients are still suffering from their disease. We should not forget how impactful it is to hear that you have a chronic disease.”

– Healthcare Professional

“My dream is that we can cure Rheumatoid Arthritis and other rheumatic diseases.”

– Healthcare Professional

Assumptions

To quantify the treatment effect of bDMARDs and the associated patient experience, we used the following **assumptions**:

1. All bDMARDs cause improvement of the DAS28 score, and this can be considered to be a class effect
2. Improvements in DAS score represent symptom reduction and improved patient-reported health. These improvements cascade into additional benefits, such as better physical functioning, improvement quality of life, etc.
3. The additional benefits of bDMARDs are also considered to be a class effect

Reference list

Research articles

- Boyadzieva, et al. Quality of Life and Cost Study of Rheumatoid Arthritis Therapy With Biological Medicines. *Front Pharmacol* 2018; **9**: 794.
- Emery, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 2008; **372**(9636):375-382.
- Huscher, et al. Evolution of cost structures in rheumatoid arthritis. *Ann Rheum Dis* 2015; **74**(4):738-745.
- Kaló, et al. Patient access to reimbursed biological disease-modifying antirheumatic drugs in the European region. *J Market Access & Health Policy* 2017; **5**:1345580.
- Kavanaugh, et al. Effect of Certolizumab Pegol With Methotrexate on Home and Work Place Productivity and Social Activities in Patients With Active Rheumatoid Arthritis. *Arthritis Rheum* 2009; **61**(11):1592-1600.
- Minichiello, et al. Time trends in the incidence, prevalence, and severity of rheumatoid arthritis: A systematic literature review. *Joint Bone Spine* 2016; **83**(6):625-630.
- Salaffi et al. Radiographic scoring methods in rheumatoid arthritis and psoriatic arthritis. *Radiol Med* 2019; **124**:1071–1086.
- van Riel & Renskers. The Disease Activity Score (DAS) and the Disease Activity Score using 28 joint counts (DAS28) in the management of rheumatoid arthritis. *Clin Exp Rheumatol* 2016; **34**(5 Suppl 101):S40-S44.

Reports

- NICE Technology Assessment Report TA375 <https://www.nice.org.uk/guidance/ta375/documents/rheumatoid-arthritis-adalimumab-etanercept-infliximab-certolizumab-pegol-golimumab-abatacept-and-tocilizumab-review-assessment-report2> Accessed July '22

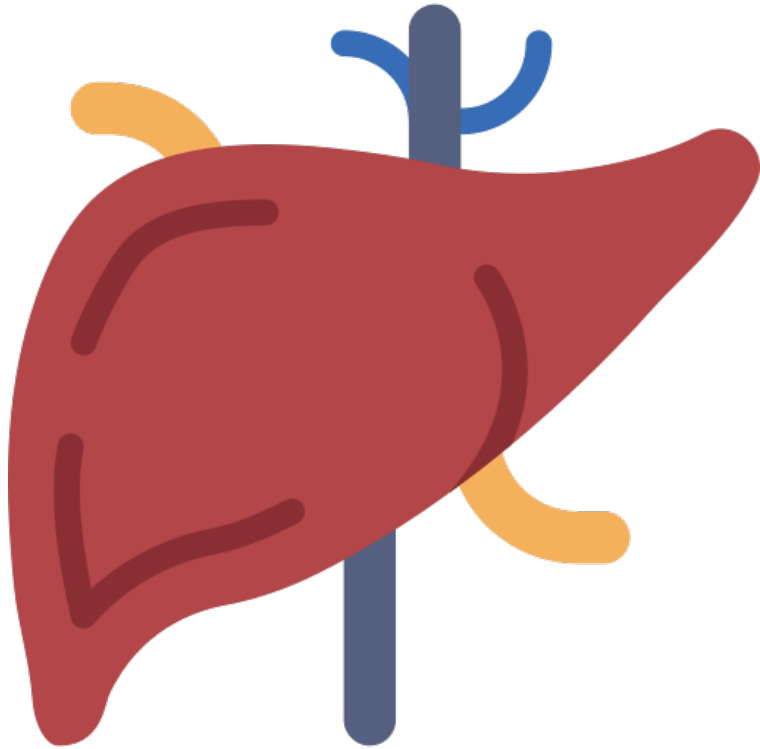
Website sites

- EuroQol, EQ 5D. <https://euroqol.org/> Accessed August '22
- Arthritis Health, Disease Activity Scores (DAS and DAS28) Definition. [https://www.arthritis-health.com/glossary/disease-activity-scores-das-and-das28#:~:text=A%20Disease%20Activity%20Score%20\(DAS,and%20joint%20swelling%20and%20tenderness.](https://www.arthritis-health.com/glossary/disease-activity-scores-das-and-das28#:~:text=A%20Disease%20Activity%20Score%20(DAS,and%20joint%20swelling%20and%20tenderness.) Accessed July '22
- Healthline, Rheumatoid Arthritis by the Numbers: Facts, Statistics, and You. <https://www.healthline.com/health/rheumatoid-arthritis/facts-statistics-infographic#Complications> Accessed July '22
- Rheumatology Usherbrooke, Sharp van der Heijde Score. <http://rheumatology.usherbrooke.ca/?q=scoressharp> Accessed August '22
- Lavender, 2021. <https://www.self.com/story/rheumatoid-arthritis-medication-changes> Accessed July '22
- DAS28, DAS28 score. <https://www.das-score.nl/nl-nl/uitleg-das28/das28-score> Accessed August '22
- LUMC Reumatologie, Historie van de afdeling. <https://www.lumc.nl/org/reumatologie/contact/Historie/> Accessed August '22

Interviews

Interviews conducted in July and August 2022 with 1 Patient Advocate and 2 Healthcare Professionals (KOLs)

The DAAs: a paradigm shift in chronic Hepatitis C treatment



CASE OUTLINE

- I. **Case for change**
 - *Situation*
 - *Challenge*
 - *Paradigm shift*
 - *Patient population*
- II. **Value to patients**
- III. **Value to the healthcare system**
- IV. **Value to society**
- V. **Annex**
 - *Key assumptions*
 - *Reference list*

Case summary | Hepatitis C

The DAAs: a paradigm shift in chronic Hepatitis C treatment

CASE FOR CHANGE



- **Situation** – Hepatitis C is a cancer-causing virus of growing public health concern that places a large burden on local health systems and economies
- **Challenge** – Early treatment options posed significant efficacy and tolerability challenges for HCPs and patients
- **Paradigm shift** – First- and second-generation direct-acting antivirals (DAAs) have revolutionized HCV treatment
- **Population** – Hepatitis C is a worldwide health challenge, with approx. 14 M patients infected in the European Region

VALUE FOR PATIENTS



- **A cure for most patients** – DAA treatments offer efficacy rates (>98%) approaching cure
- **Prevented disease progression** – Near-curative DAA treatment can prevent advanced liver disease and liver-related death in many patients
- **Improved Quality of Life** – DAA treatment can also reduce the number of patients with additional health problems associated with chronic HCV

VALUE TO THE HEALTHCARE SYSTEM



- **Preventable resource use** – Expanded access to DAA treatment for chronic Hepatitis C could lead to significant savings for EU healthcare systems
- **Averted liver events** – DAA treatment has reduced the proportion of transplants due to HCV-related liver disease

VALUE TO SOCIETY



- **Getting patients able to work again** – DAA treatment improves work productivity and reduces days of sick leave in patients with chronic Hepatitis C
- **Economic gain** – Improved work productivity due to DAA treatment translates to annual savings of €749 to €1,112 per employed patient (deep dive in 4 countries)
- **Benefits outweigh costs** – The DAA list price is offset by a reduction in multiple other healthcare costs, leading to a saving for society of €11,000 per patient (deep dive in Belgium)

TOWARDS THE FUTURE



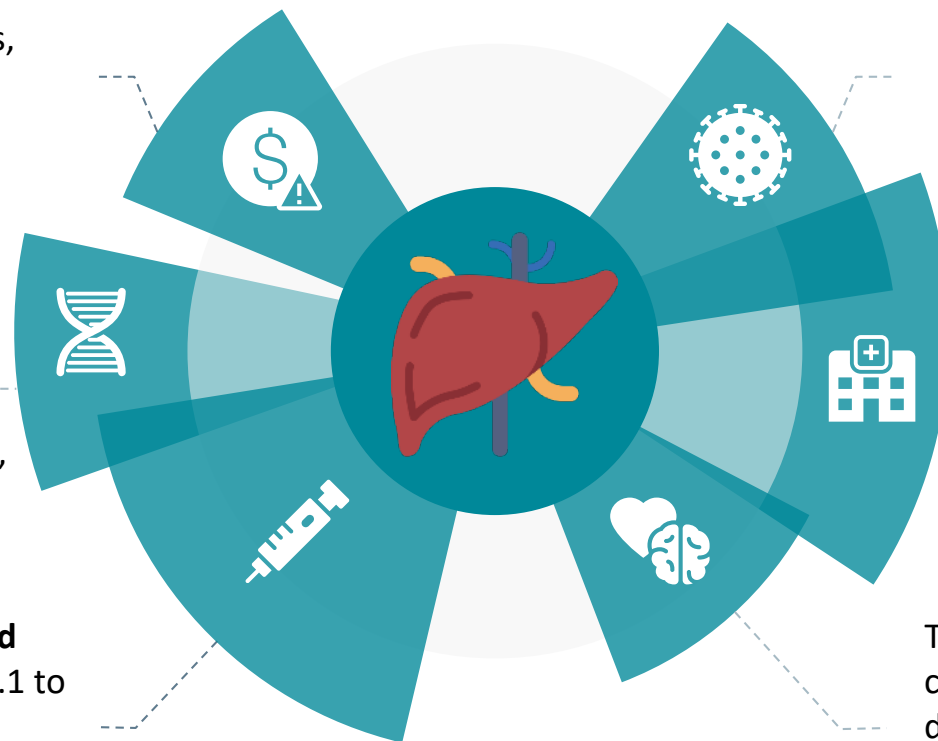
- **Working towards HCV elimination** – The WHO goal of eliminating Hepatitis C by 2030 is now feasible because of DAAs, but the unmet need is now in finding and treating the undiagnosed, thereby maximizing the value of DAA cure

Hepatitis C is a cancer-causing virus of growing public health concern that places a large burden on local health systems and economies

The **burden of Hepatitis C** is influenced by country-specific factors, such as local epidemiology, historical and present risk factors, local screening programs, treatment guidelines and treatment access^{4,5}

There are **6 Hepatitis C virus genotypes**, with G1 and G3 being most common in Western Europe (55% and 29% prevalence, respectively)^{*4}

Hepatitis C is **more commonly reported among men** (male-to-female ratio of 2.1 to 1), and the most affected age group in both sexes is 25–34 years. **Injecting drug use** accounts for 45% of cases with reported transmission mode³



Hepatitis C is a **slow, bloodborne viral disease** that causes **inflammation of the liver**¹. Initial symptoms are vague but could include fatigue, and as the disease progresses, **liver complications** such as cirrhosis (a lengthy process) and liver cancer could arise¹

Hepatitis C is a **leading cause of liver cancer** (hepatocellular carcinoma) and liver transplants worldwide²

The **psycho-emotional impact** of Hepatitis C can be severe, as the fatigue can lead to depression, and on to reduced work productivity and unemployment¹

1. SEBOIO 2020.
2. THE EUROPEAN UNION HCV COLLABORATORS 2017.
3. ECDC 2019.
4. PETRUZZIELLO ET AL. 2016.
5. MENNINI, ET AL. 2021.

*COUNTRIES STUDIED WERE AUSTRIA, BELGIUM, CYPRUS, DENMARK, FINLAND, GERMANY, GREECE, ICELAND, IRELAND, ITALY, LUXEMBOURG, THE NETHERLANDS, NORWAY, PORTUGAL, SPAIN, SWEDEN, SWITZERLAND AND THE UK. NB PREVALENCE FIGURES ARE PRE ARRIVAL OF DAA TREATMENTS.

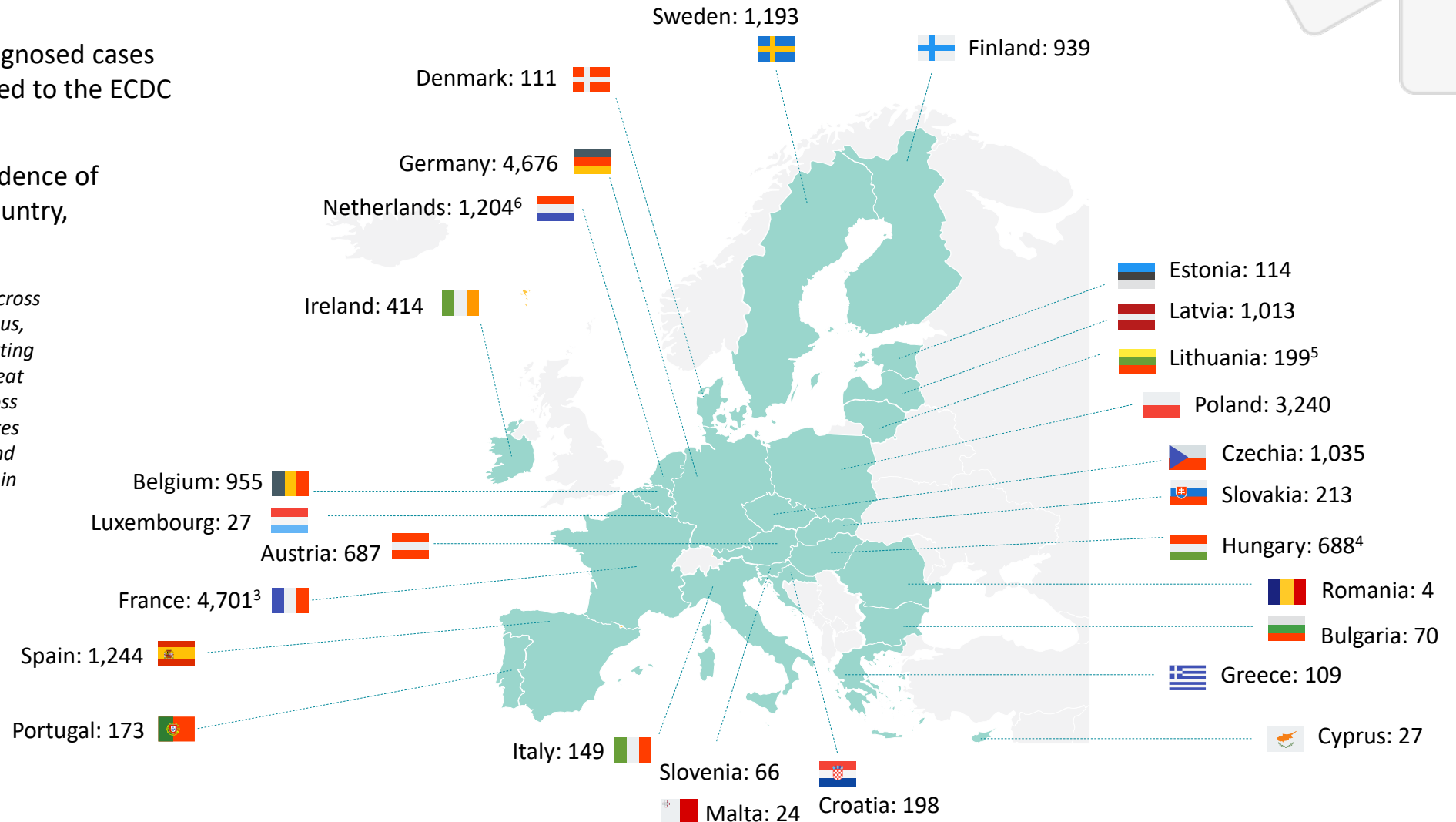
Hepatitis C is a worldwide health challenge, with approx. 14 M patients infected in the European Region¹

The number of newly diagnosed cases (incidence rate) is reported to the ECDC each year²

The map here shows incidence of **chronic HCV** per EU27 country, reported in 2019²

Note: HCV Surveillance systems across the EU countries are heterogeneous, leading to inconsistent case reporting methods. This may explain the great variation in relative numbers across countries. Overall, notification rates were mostly higher in northern and western European countries than in southern European countries⁴

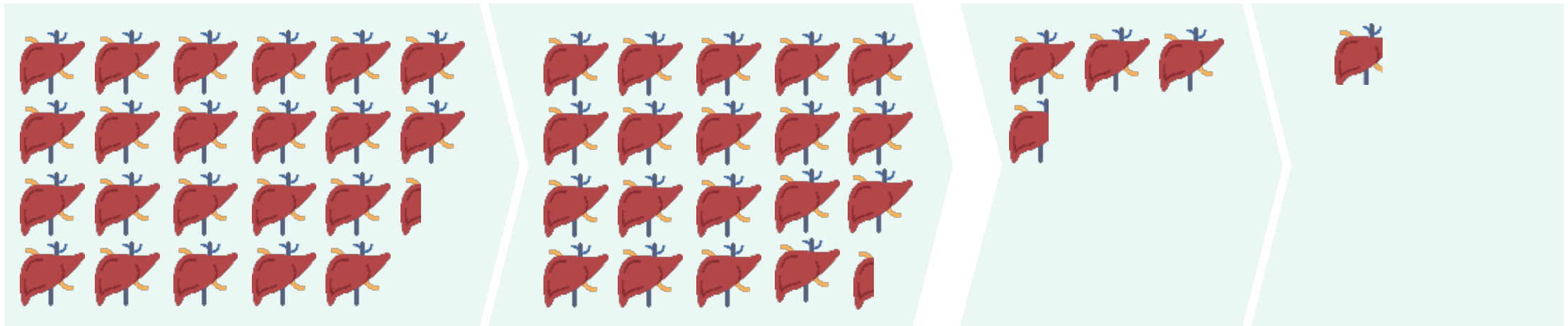
For the purposes of this case study, we will focus on EU27, wherever possible



1. WHO, 2022.
 2. ECDC 2019.
 3. OECD, 2019A.
 4. OECD, 2019B.
 5. OECD, 2019C.
 6. OECD, 2019D.

WHO EUROPEAN REGION COMPRISES 53 COUNTRIES. CURRENT PREVALENCE UNAVAILABLE FOR EU27 ONLY.
 ECDC: EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL. ECDC SOURCE EXCLUDED FRANCE, LITHUANIA, HUNGARY, NETHERLANDS.

If left untreated, Hepatitis C can lead to serious health consequences



Chronic Hepatitis C

An estimated **22,379** people per year across EU27 are newly diagnosed per year with chronic Hepatitis C (CHCV)¹⁻⁵

Chronic liver disease

On average, **19,395** of these chronic Hepatitis C patients go on to develop chronic liver disease⁶

Cirrhosis

If left untreated, **3,730** go on to develop cirrhosis over a 20-30 year timeframe⁶

Death due to HCV-related cirrhosis / liver cancer

Of these, if left untreated, **895** die of Hepatitis C-related cirrhosis or liver cancer⁶

“There is the psychological aspect as well. If you’re carrying an infectious virus that is transmitted by contact.. You have a leper feeling that you can’t touch people, share things with people. How you interact as a human becomes very different. You feel you have a blight on your future, as to what’s going to happen – ‘Do I have a life in the future or not? Is this going to kill me? How quickly will it kill me?’”

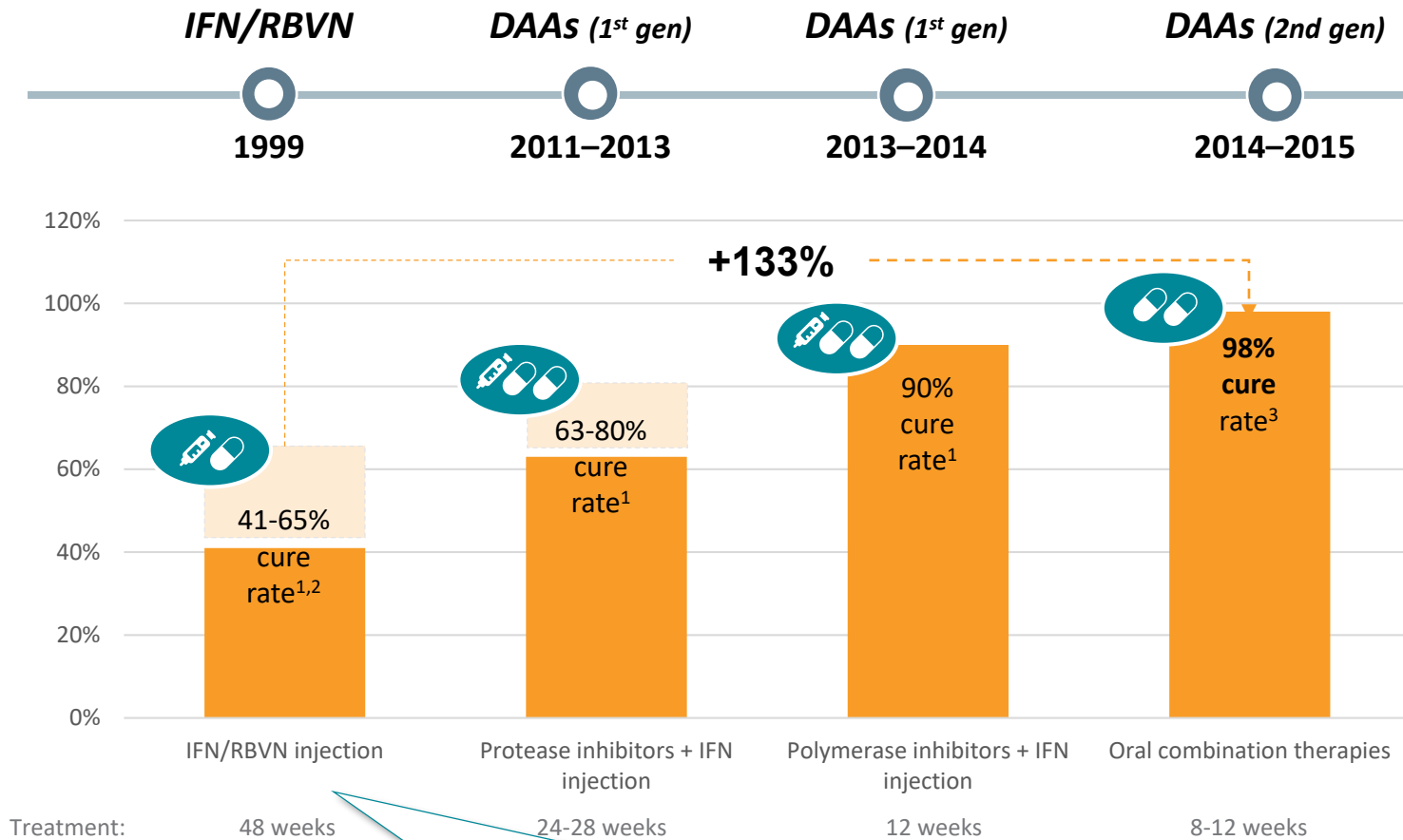
-- Dr John Dillon, University of Dundee, UK

1. ECDC 2019.
2. OECD, 2019A.
3. OECD, 2019B.
4. OECD, 2019C.
5. OECD, 2019D.
6. EMCDDA, 2016.



= 1000 people

Early treatment options posed challenges for HCPs and patients – but DAAs have revolutionized HCV treatment by offering a near-cure



“The big change came when we had interferon-free regimens. They were revolutionary. We could treat almost everybody.”
 -- Dr John Dillon, University of Dundee, UK

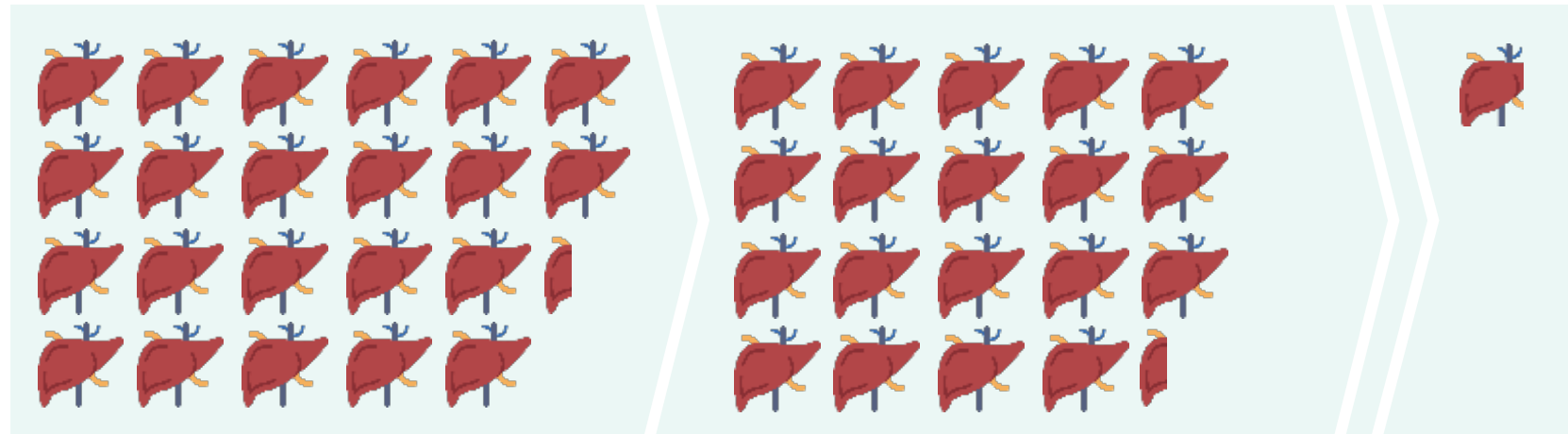
“In 2013, we knew that the cure for more than 90% of the people was there. Not only going from 50% to 95% of cure, but also people who would not respond to interferon were now eligible for these drugs. Disruptive innovation. There was no comparison between what we had and what we got.”
 -- Luís Mendão, Co-Chair, ACHIEVE, Portugal

“We’ve moved to the point where... do I really need to bother to teach the medical students and junior doctors about Hepatitis C because they will never see it!”
 -- Dr John Dillon, University of Dundee, UK

“The physical pain was overwhelming. My body was in pain, sometimes I was losing hair, sometimes my hands were bleeding. It was pretty awful.”
 -- George Kalamitsis, Chairman, Prometheus Hellenic Liver Patient Association, Greece

1. PHRMA, 2017.
 2. LUO, ET AL. 2019.
 3. MANNIS & MAASOUMY, 2022.

Near-curative DAA treatment can prevent the development of advanced liver disease and liver-related death in significant numbers of patients



Chronic Hepatitis C

Of the estimated **22,379** people per year across EU27 who are newly diagnosed per year with chronic HCV, given the DAA 98% cure rate ...¹⁻⁵

If treated with DAAs:

Advanced liver disease

19,007 patients could be prevented from developing advanced liver disease...¹⁻⁶

Death

And **877** could be prevented from dying from Hepatitis C-related cirrhosis or liver cancer¹⁻⁶



Moreover, when patients are diagnosed in a late stadium DAA therapy has been associated with **regression of cirrhosis in >50%**⁷

"It's little short of miraculous. The set of drugs that were so easy to take, so effective, just changed the natural history of this disease completely."

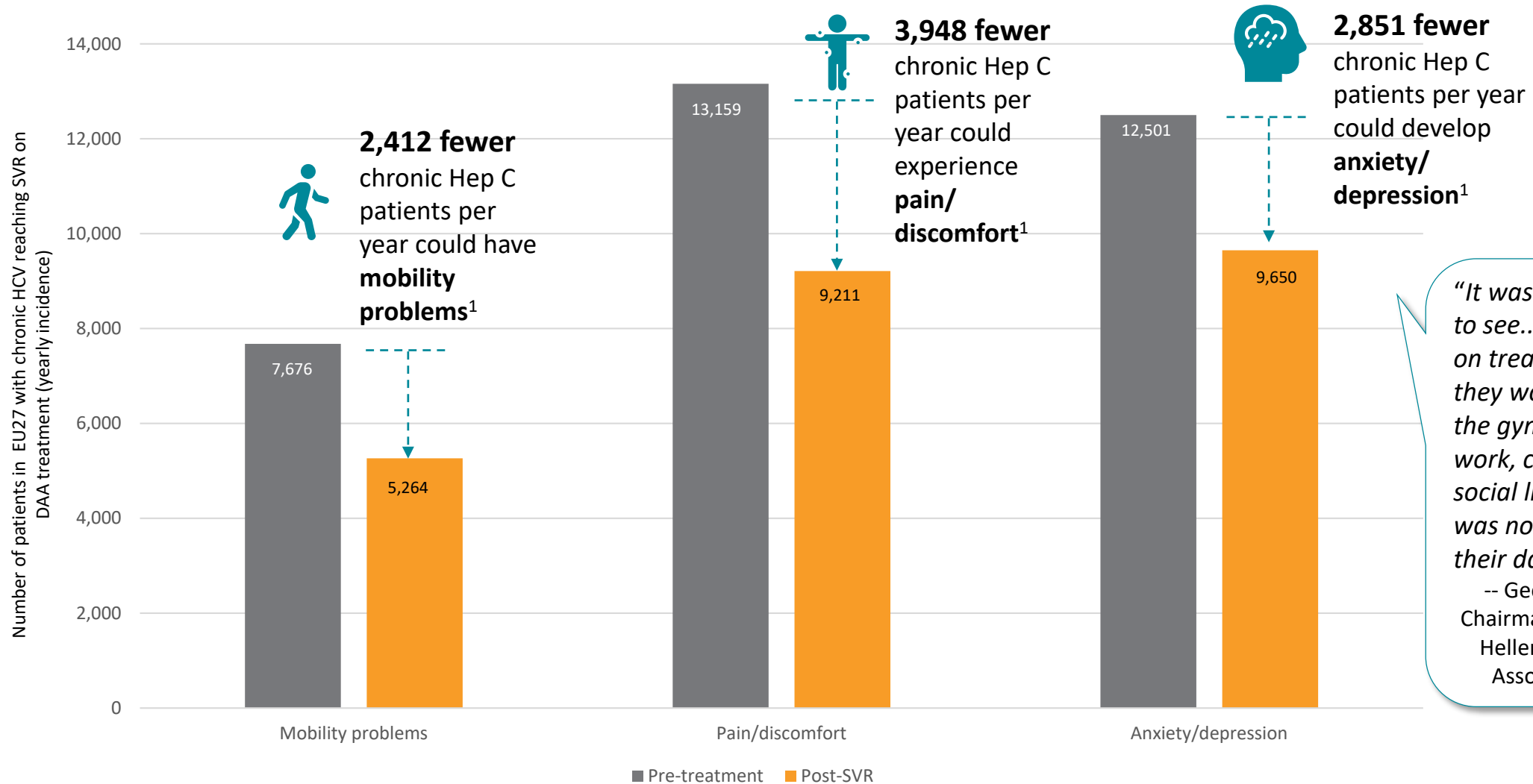
-- Dr John Dillon, University of Dundee, UK

1. ECDC 2019.
2. OECD, 2019A.
3. OECD, 2019B.
4. OECD, 2019C.
5. OECD, 2019D.
6. EMCDDA, 2016.
7. DURAND & FRANCOZ, 2017.



= 1000 people

Near-curative DAA treatment can also reduce the number of patients who have additional health problems associated with chronic HCV



“It was fascinating to see.. people were on treatment and they would go to the gym, go to work, continue their social life. Illness was not affecting their daily routine.”

*-- George Kalamitsis,
Chairman, Prometheus
Hellenic Liver Patient
Association, Greece*

1. JUANBELTZ, ET AL. 2018.

Expanded access to DAA treatment for chronic Hepatitis C could lead to significant savings for healthcare systems across Europe



Deep dive into Romania, Italy and Spain



Expanded access (i.e. without restrictions, so that patients in early stages of infection can receive treatment) to DAA treatment can lead, **over a 20-year time horizon**, to¹:



Over a 20-year time horizon:



Healthcare cost savings

€45M

€63M

€275M

..as a result of avoided hepatocellular carcinoma, decompensated cirrhosis and liver transplants



Time to recovery of investment*

6.7 years

5.4 years

4.5 years

Time to return of investment is generally related to two factors: DAA cost and liver disease costs.

These countries illustrate the varying epidemiological patterns and case reporting of chronic infection across EU27²:

Cases per year	4	149	1,244
% of EU27 (annual incidence)	0.02%	0.7%	5.6%

1. MENNINI, ET AL. 2021.
2. ECDC 2019.

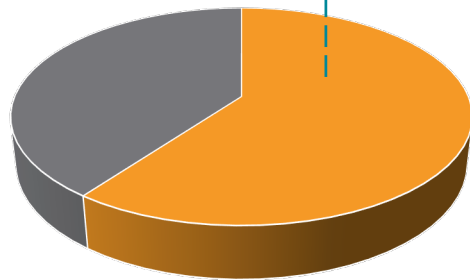
*BREAK-EVEN POINT REALISING RETURN ON INVESTMENT. GENERALLY RELATED TO DAA COST AND LIVER DISEASE COSTS. AVERAGE COST OF DAA TREATMENT WAS ESTIMATED USING EXPERT OPINION AND NON-OFFICIAL SOURCES. SEE SLIDE NOTES FOR COSTS USED IN EACH COUNTRY. NOTE: THE COST OF DAAS ADMINISTERED TO PATIENTS IN 2015-2016 WAS HIGHER THAN THAT ADMINISTERED TO PATIENTS IN 2017-2019, SUGGESTING THAT THE DECREASE IN RETURN ON INVESTMENT OVER TIME WAS ALSO BECAUSE OF THE DECREASING PRICE OF TREATMENT.

DAA treatment has reduced the proportion of transplants due to HCV-related liver disease



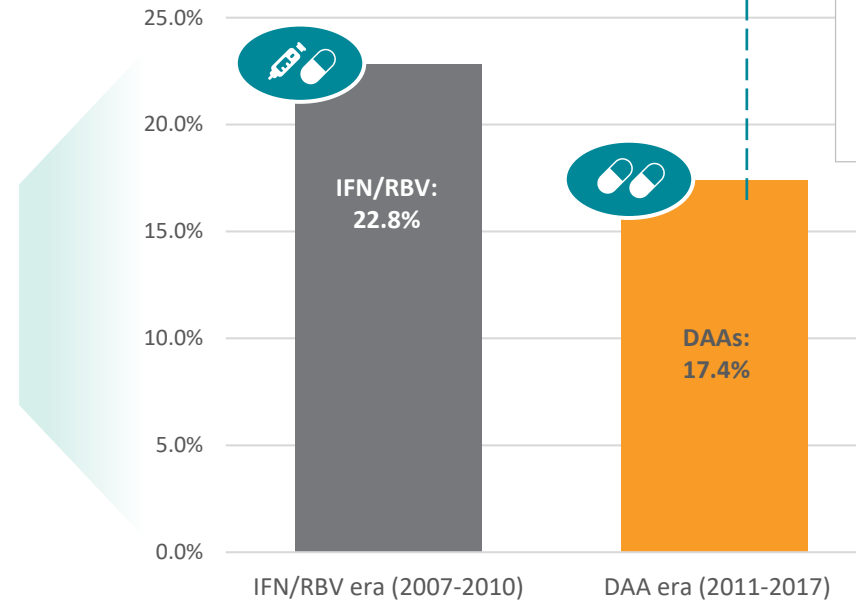
60,527 liver transplants were performed in Europe between 2007 and 2017*¹

Of these, **36,832 (60%)** included patients with chronic HCV**¹

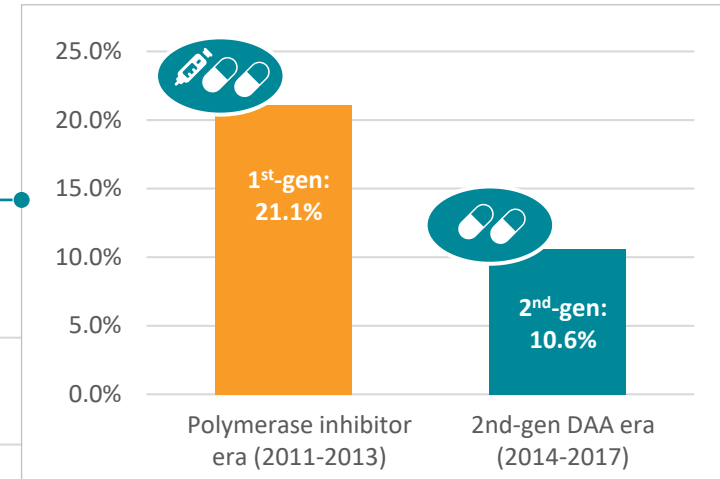


■ Liver transplants incl HCV ■ Other liver transplants

% of liver transplants due to HCV liver disease decreased from 22.8% when IFN/RBV was standard treatment, to 17.4% when DAAs were used¹



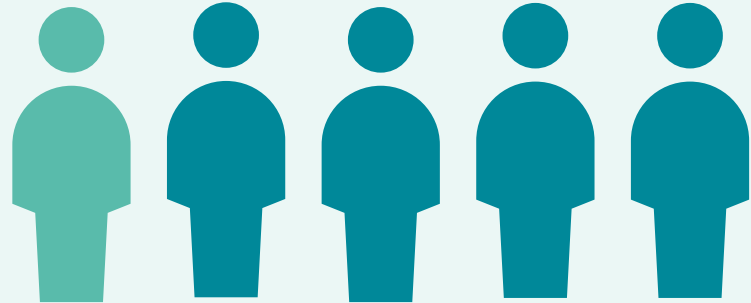
Liver transplants due to HCV-related liver disease during different eras of treatment availability¹



2nd-gen DAAs led to only 10.6% of liver transplants due to HCV[†], compared with 21.1% with polymerase inhibitors¹

*EUROPEAN COUNTRIES IN STUDY WERE NOT NAMED. ASSUME THEY INCLUDE THE UK. **ALSO INCLUDES HEPATITIS B, ALCOHOLIC (ETOH) AND NON-ALCOHOLIC STEATOHEPATITIS (NASH); DATA NOT SEPARATED OUT. †DECOMPENSATED HCV AND HEPATOCELLULAR CARCINOMA INDICATIONS
1. BELLI, ET AL. 2018

DAA's will continue to reduce the need for liver transplants due to HCV-related liver disease



1 in 5 patients with advanced liver disease who are treated with DAAs could be delisted from the liver transplant waiting list¹

DAAs will continue to reduce the need for liver transplants in HCV-infected patients, and the proportion of HCV-infected patients who are candidates for liver transplant will continue to decrease in the future²

"Patients came off transplant lists because their virus went away, their livers got better. Patients that you thought were going to end up transplanted within a year or two were cured."

-- Dr John Dillon, University of Dundee, UK

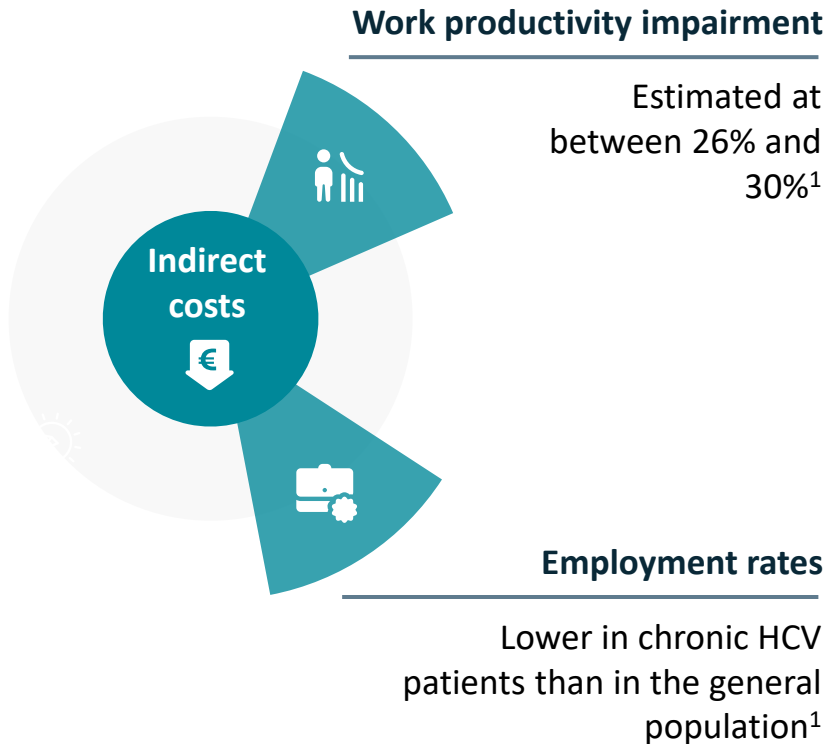


The reduction in HCV-related reasons for liver transplants means **at least 600 more livers per year** could be redistributed to European* patients with indications other than HCV³

1. BELLI, ET AL. 2016.
2. DURAND & FRANCOZ, 2017.
3. BELLI, ET AL. 2018.

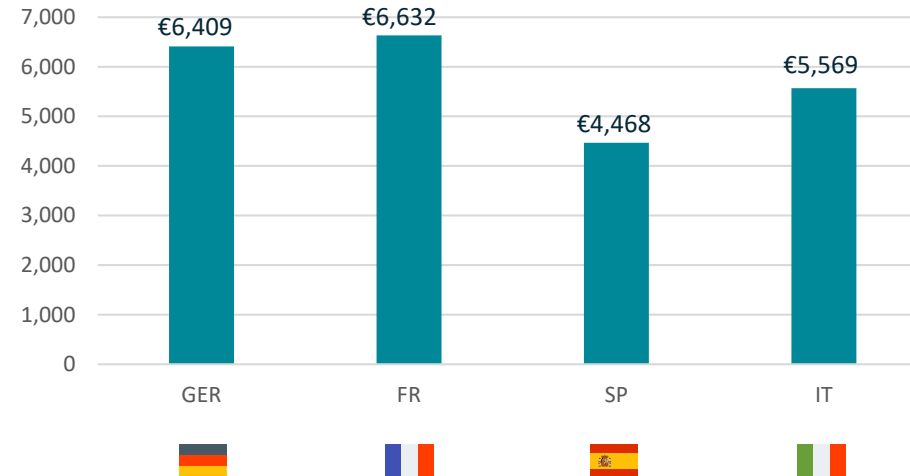
*ANALYSIS BASED ON DATA FROM THE EUROPEAN LIVER TRANSPLANT REGISTRY, WHICH INCLUDES GREAT BRITAIN AND SOME EUROPEAN COUNTRIES OUTSIDE OF EU27

Chronic HCV infection imposes a great economic burden on patients, their employers and society

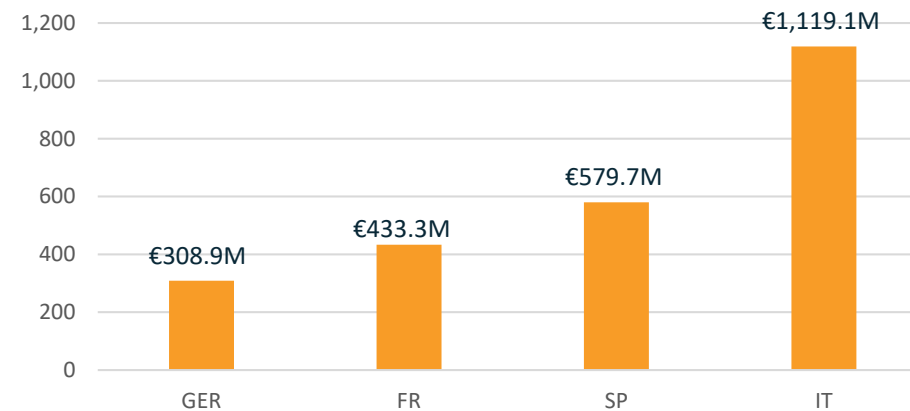


Value of lost production*¹:
Country Deep Dives:

Annualised loss per employed HCV patient (€)

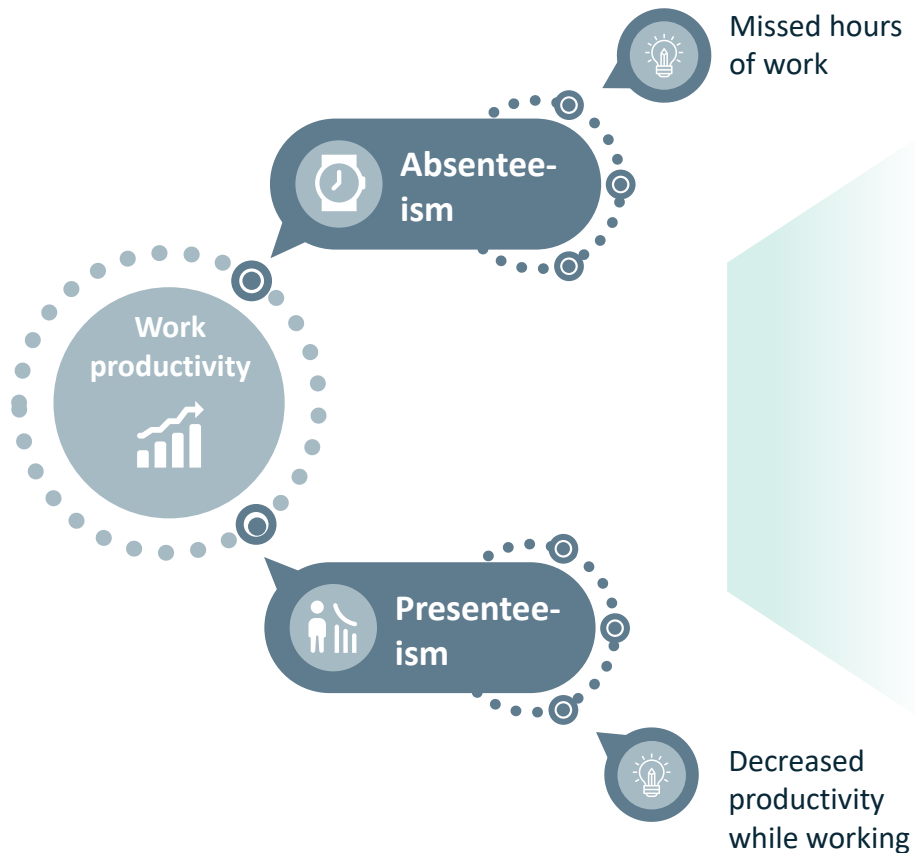


Annual aggregate loss in WP (€)

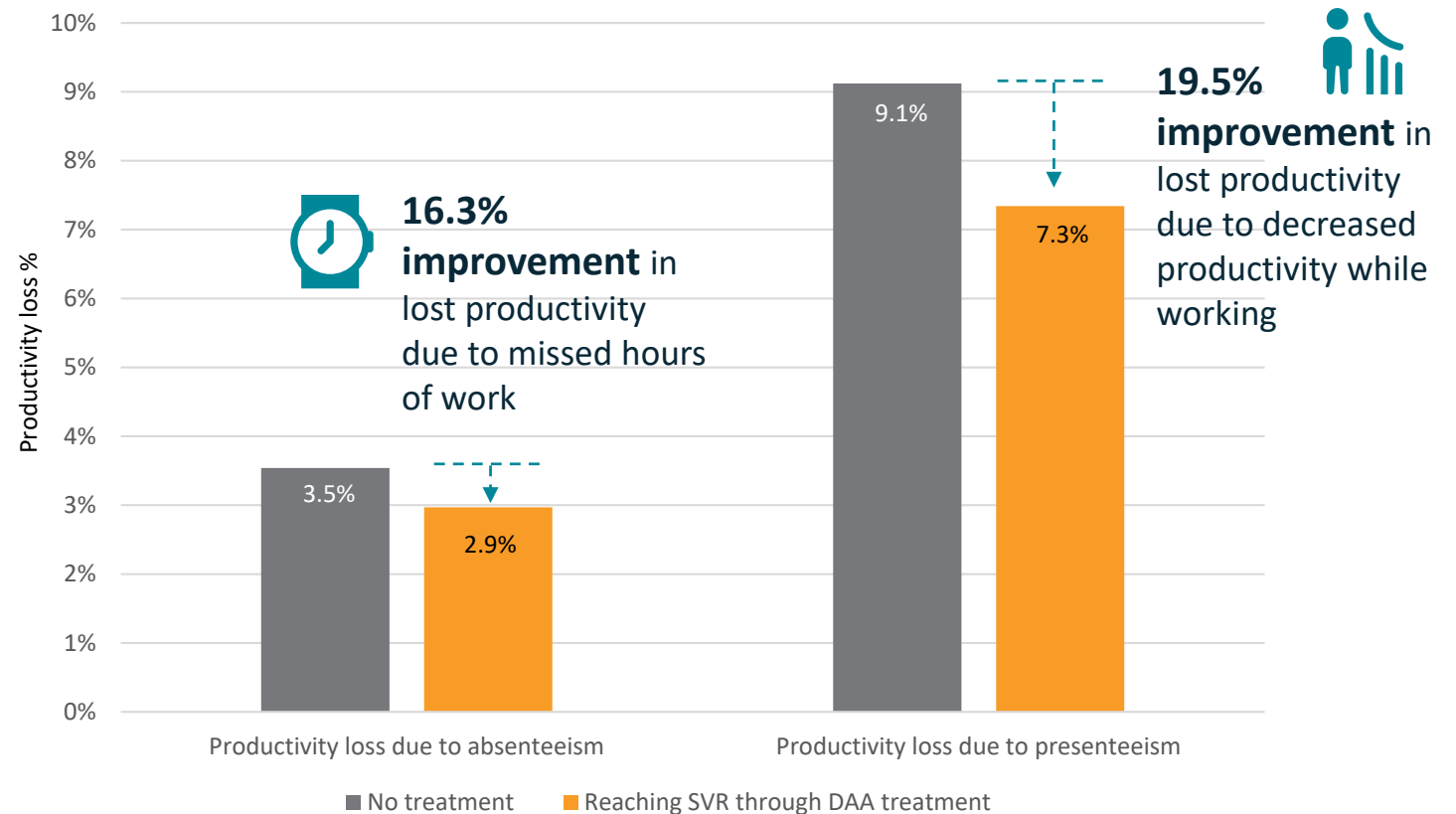


WP: WORK PRODUCTIVITY. *STUDY FOCUSED ON PATIENTS WITH CHRONIC HEPATITIS C GENOTYPE 1
1. YOUNOSSI, ET AL. 2016.

DAA treatment improves work productivity in patients with chronic Hepatitis C by 16-20%



Impact of DAA treatment on work productivity impairment*



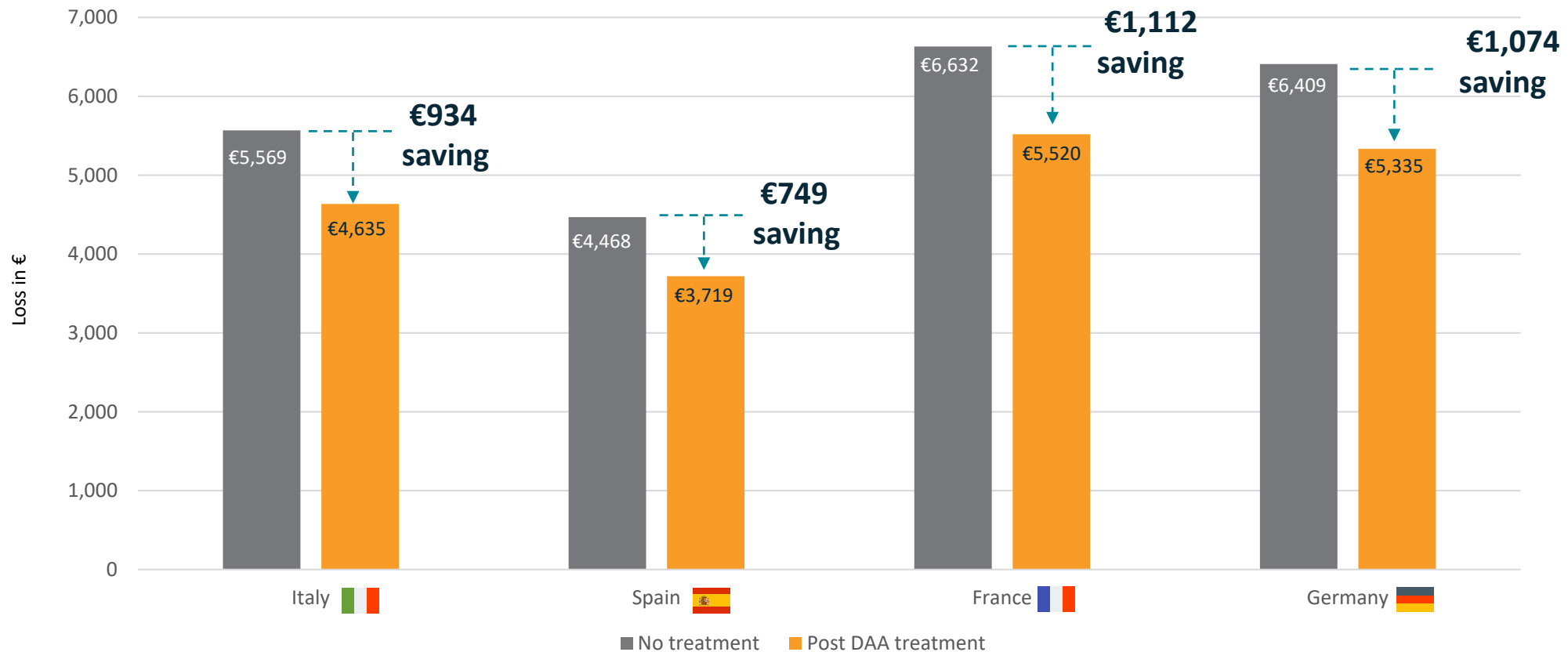
*DATA FROM 5 EU COUNTRIES: ITALY, SPAIN, FRANCE, GERMANY, UK. UK DATA NOT REPORTED SEPARATELY. ACTUAL NUMBERS OF DAYS LOST WERE NOT REPORTED
1. YOUNOSSI, ET AL. 2016.



Deep Dive: Improved work productivity due to DAA treatment translates to annual savings of €749 to €1,112 per employed patient across 4 EU countries

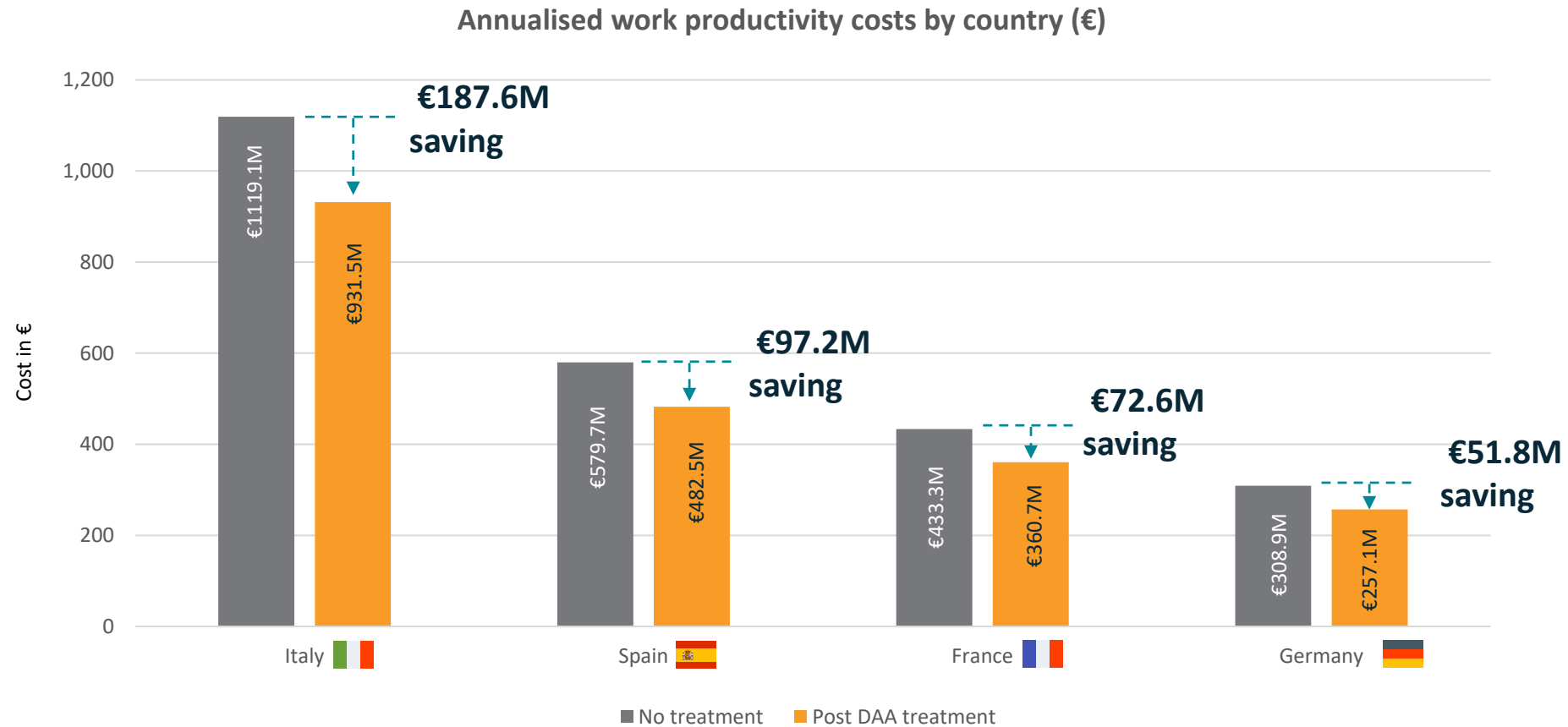


Annualised loss per employed HCV patient by country (€)





Deep Dive: The annualised per-employed-patient savings translate to annual aggregate savings of €52M to €188M across 4 EU countries

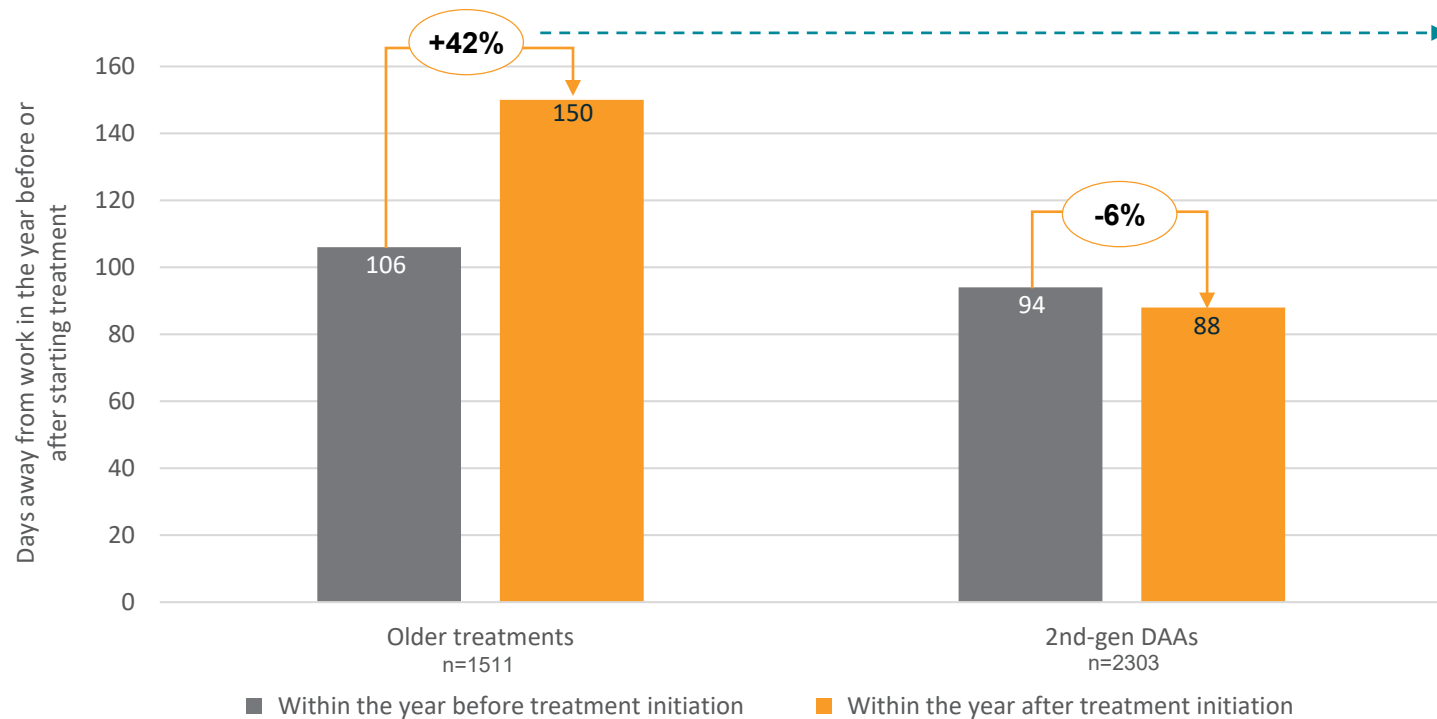


Deep Dive: 2nd-gen DAA treatment reduces days of sick leave



Deep dive into Sweden

Patients treated with 2nd-gen DAAs without peg-IFN experience **fewer days away due to sick leave** in the year after starting treatment, compared with older HCV treatments¹:

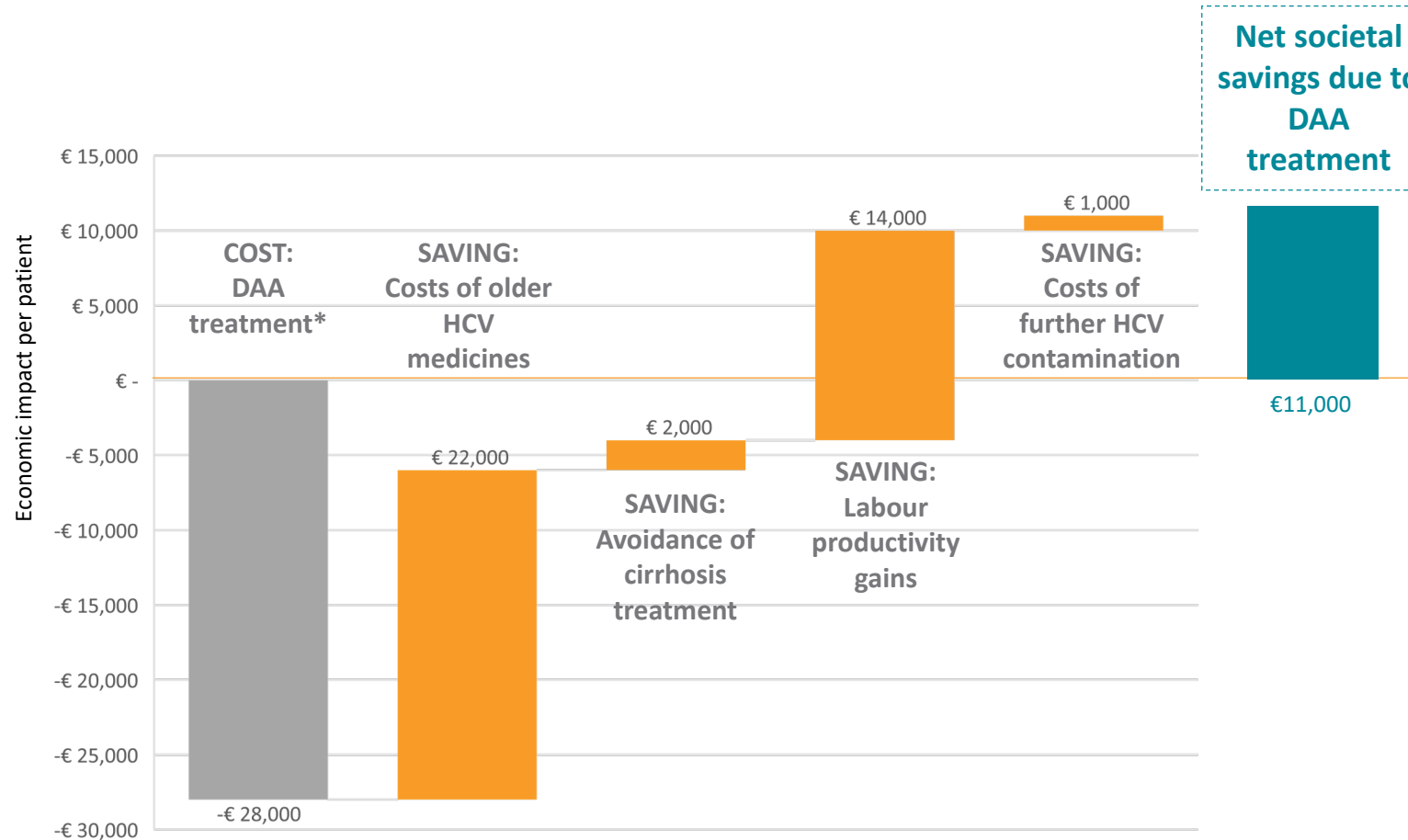


Avoidable 42% increase in number of days away from work in patients treated with 2nd-gen DAAs vs older treatments¹

One possible reason for the reduction in days away from work with DAAs is the reduced burden of adverse events with these drugs¹:

1. LINDGREN, ET AL. 2021.

Deep Dive: The DAA costs is offset by savings made in other healthcare costs, leading to a net saving for society of €11,000 per patient



Net societal savings due to DAA treatment → **€146M** total eventual savings to Belgium society on a population basis¹

“When the DAAs first came out, they were very expensive and there was a big jump in cost. We were treating patients who were about to incur huge health costs. So we were averting substantial costs... Because of countries agreeing to treat larger volumes of patients, the cost fell. For that fixed sum that the healthcare system could invest, they could treat a lot more patients.”

-- Dr John Dillon, University of Dundee, UK

Further, Hepatitis C infections are a driver of liver transplants costs in Belgium – if these could be avoided, **another €6M per year** could be saved for Belgium¹

DEEP DIVE IN BELGIUM. ORANGE LINE MEANS BREAK EVEN POINT. *USES LIST PRICE BETWEEN €24,000 AND €30,000. 1. SEBOIO 2020.

Eliminating Hepatitis C by 2030 is the WHO goal, but the unmet need is in finding and treating the undiagnosed, thereby maximizing the value of DAA cure

World Health Organization Global Health Sector Strategy (GHSS) set goal of eliminating viral hepatitis by 2030¹

- 90% reduction in incidence
- 65% reduction in mortality

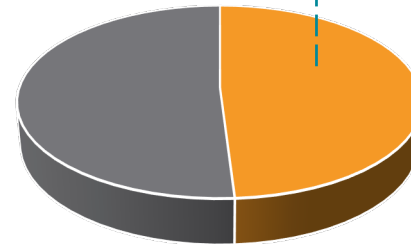
The reduction in liver-related deaths is now feasible because of the availability of DAAs, which have shown a high rate of sustained viral response²

-- The European Union HCV Collaborators

However, the long-term value of the DAAs could be significantly weakened if the undiagnosed population of HCV-infected is not identified and treated

“Globally, we are not on track. We need to estimate how many are not diagnosed. Our struggle now is to get the data right to see what is working.. to not fly blind. We need 90% of the people living with Hep C diagnosed. If we don't have an estimation of how many there are, how can we say that 90% are diagnosed and 90% treated?”

-- Luís Mendão, Co-Chair, ACHIEVE, Portugal



49%

Of HCV-infection injecting drug users have been estimated to be **undiagnosed** in 5 countries*³

The undiagnosed general population must also be considered

For new treatment developments to have any significant impact on HCV mortality and population prevalence, finding and screening HCV cases needs crucially to be improved⁴

1. WHO, 2022.
2. THE EUROPEAN UNION HCV COLLABORATORS, 2017.
3. DILLON, ET AL. 2016.
4. HARRIS, ET AL. 2016.

*DENMARK, FRANCE, POLAND, SPAIN, UK

Hepatitis C case study

Calculation assumptions

Assumption 1

Risk of progression to different disease stages with hepatitis C infection was based on data from the EMCDC¹. Calculations assumed that:

- For every 100 people with Hepatitis C virus, 75-80 will develop chronic infection
- Of the 100 people with Hepatitis C, 60-70 will develop chronic liver disease
- Of the 100 people with Hepatitis C, 5-20 will develop cirrhosis over a period of 20 years
- Of the 100 people with hepatitis C, 1-5 will die of cirrhosis or liver cancer

Assumption 2

Case reporting (incidence) by country was taken from the ECDC². Some countries differentiated their cases into chronic and acute cases, and some also reported unknown cases, whereas other countries reported all cases as an undifferentiated total figure. Overall, the ECDC reported that 6% of cases were reported as acute, 22% as chronic, 69% as unknown, and 3% as unclassified.

In our calculations we have accounted for the Unknown cases, as we must assume that a proportion of them must be chronic cases. We have applied the proportions of acute/chronic etc by scaling them up to the total cases across EU27.

To do this, we took the numbers of known acute and chronic cases to be a 'sample' of the total number of reported cases in EU27, and calculated what the proportions would be scaled-up to that total population. We then applied these scaled-up proportions to the total number of reported cases in EU27. See accompanying Excel calculation sheet for full details.

We also used these scaled-up proportions to calculate the numbers of chronic cases in countries where only unknowns or All cases were reported. In countries where chronic and acute cases were reported alongside unknown cases, to discover the number of unknown cases that should be chronic, we calculated the country-specific proportion of acute and chronic cases from the known case reports, and used that instead. See accompanying Excel calculation sheet for all calculations.

Full reference list

Research articles

- Belli LS, et al. Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: A European study. *J Hepatol* 2016; **65**(3):524-531.
- Belli LS, et al. Impact of DAAs on liver transplantation: Major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. *J Hepatol* 2018; **69**(4):810-817.
- Dillon F, et al. Urgent action to fight hepatitis C in people who inject drugs in Europe. *Hepatology, Medicine and Policy* 2016; **1**:2.
- Durand F, Francoz C. The future of liver transplantation for viral hepatitis. *Liver International* 2017; **37**(Suppl 1):130-135.
- Harris M, et al. Finding the undiagnosed: a qualitative exploration of hepatitis C diagnosis delay in the United Kingdom. *J Viral Hepatitis* 2016; **23**:479-486.
- Juanbeltz R, et al. Impact of successful treatment with direct acting antiviral agents on health-related quality of life in chronic hepatitis C patients. *PLoS One* 2018; **13**(10):e0205277.
- Lindgren P, et al. Reduced work absenteeism in patients with hepatitis C treated with second-generation direct-acting antivirals. *J Viral Hepatol* 2021; **28**:142–146.
- Luo A, et al. Efficacy and safety of direct-acting antiviral therapy for chronic hepatitis C genotype 6: A meta-analysis. *Medicine* 2019; **98**:20(e15626).
- Manns M, Maasoumy B. Breakthroughs in hepatitis C research: from discovery to cure. *Nat Rev Gastroenterol Hepatol* 2022; **19**:533-550. <https://doi.org/10.1038/s41575-022-00608-8>.
- Mennini FS, et al. The impact of direct acting antivirals on hepatitis C virus disease burden and associated costs in four European countries. *Liver International* 2021; **41**:934-948.
- Petruzzello A, et al. Hepatitis C virus (HCV) genotypes distribution: an epidemiological update in Europe. *Infectious Agents and Cancer* 2016; **11**:53.
- The European Union HCV Collaborators. Hepatitis C virus prevalence and level of intervention required to achieve the WHO targets for elimination in the European Union by 2030: a modelling study. *Lancet Gastroenterol Hepatol* 2017; **2**:325–336.
- Younossi Z, et al. Impact of eradicating hepatitis C virus on the work productivity of chronic hepatitis C (CH-C) patients: an economic model from five European countries. *J Viral Hepat* 2016; **23**(3):217-226.

Reports

- SEBOIO The Value of Medicines in Belgium - Twenty Years of High Societal Impact. 2020 <https://pharma.be/sites/default/files/2021-08/value-of-medicines.pdf>
- European Centre for Disease Prevention and Control (ECDC). Hepatitis C. In: ECDC. Annual epidemiological report for 2019. Stockholm: ECDC; 2021. <https://www.ecdc.europa.eu/sites/default/files/documents/AER-Hepatitis-C-2019.pdf>
- PhRMA, Prescription Medicines: International Costs in Context (2017). <http://phrma-docs.phrma.org/files/dmfile/PhRMA-International-Costs-in-Context-2017-03-011.pdf>
- OECD. State of Health in the EU. France. Country Health Profiles. 2019. <https://www.oecd-ilibrary.org/docserver/d74dbbda-en.pdf?expires=1656000956&id=id&accname=guest&checksum=305A52D35EACFB606071529D91F970E1>
- OECD. State of Health in the EU. Hungary. Country Health Profile 2019. https://www.euro.who.int/_data/assets/pdf_file/0007/419461/Country-Health-Profile-2019-Hungary.pdf
- OECD. State of the Health in the EU. Lithuania. Country Health Profile 2019. https://www.euro.who.int/_data/assets/pdf_file/0003/419466/Country-Health-Profile-2019-Lithuania.pdf
- OECD. State of the Health in the EU. Netherlands. Country Health Profile 2019. <https://www.oecd-ilibrary.org/docserver/9ac45ee0-en.pdf?expires=1656000887&id=id&accname=guest&checksum=DE607EB6EF591B6A8C7A68E1114769E1>
- European Monitoring Centre for Drugs and Drug Addiction (2016), Hepatitis C among drug users in Europe: epidemiology, treatment and prevention, EMCDDA Insights 23, Publications Office of the European Union, Luxembourg. https://www.emcdda.europa.eu/publications/insights/hepatitis-c-among-drug-users-in-europe_en

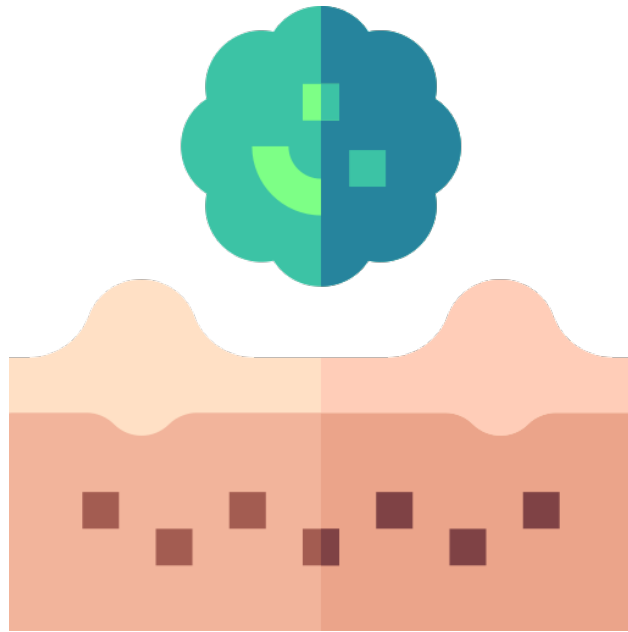
Website sites

- WHO. Hepatitis. <https://www.who.int/europe/health-topics/hepatitis> Accessed July 2022.
- WHO. Who releases first-ever global guidance for country validation of viral hepatitis B and C elimination. <https://www.who.int/news/item/25-06-2021-who-releases-first-ever-global-guidance-for-country-validation-of-viral-hepatitis-b-and-c-elimination> Accessed July 2022.

Interviews

Interviews conducted in July and August 2022 with 2 Patient Experts and 1 Healthcare Professional (KOL)

Immuno- & targeted therapy saving melanoma patient lives



CASE OUTLINE

I. Case for change

- *Situation*
- *Challenge*
- *Paradigm shift*
- *Patient population*

II. Value to patients

III. Value to the healthcare system

IV. Value to society

V. Annex

- *Key assumptions*
- *Reference list*

Case summary | Melanoma

Immuno- & targeted therapy saving melanoma patient lives

CASE FOR CHANGE



- **Situation** – Melanoma is a type of skin cancer of growing public health concern. Melanoma represents 4% of all skin cancers cases; however, it is responsible for 80% of all skin cancer deaths. This means melanoma is the most dangerous type of skin cancer. If left untreated, melanoma is deadly in most cases
- **Challenge** – Before 2011, there was no scientifically proven effective treatment for patients in stage III and IV melanoma. Therefore, survival rates were extremely low
- **Paradigm shift** – Since 2011, several immunotherapies and targeted therapies against stage III and IV melanoma were introduced in the EU27, providing the opportunity to treat melanoma, and extending life expectancy of melanoma patients significantly
- **Population** – EU27 incidence of melanoma has steadily increased over several decades. In 2020, over 116k men and women were diagnosed with melanoma. On average, 9% and 6% percent of melanoma patients have stage III and IV disease at diagnosis, respectively. However, incidence and stage distribution vary among EU countries

VALUE FOR PATIENTS



- **Preventable deaths** – Between 2011 and 2022, the survival rate for patients with stage IV melanoma has more than doubled (based on Dutch survival rates). The introduction of immunotherapies and targeted therapies against stage III and IV melanoma has reduced the number of patients dying from the disease in the first 5 years after diagnosis.

VALUE TO THE HEALTHCARE SYSTEM



- *There is limited evidence supporting an increase in value for the healthcare system from a monetary and resource use perspective related to the introduction of innovation for melanoma. The introduction of immunotherapy and targeted therapy is mainly associated with an increase in costs and resource use compared to the situation before 2011, as there were no viable treatment options back then. As such we propose to focus on value for patients and society in this case.*

VALUE TO SOCIETY



- **Reducing absenteeism** – Immunotherapies and targeted therapies increases the number of people employed after treatment for stage III and IV melanoma. Improved work productivity due to immunotherapies and targeted therapies against stage III and IV melanoma translates to productivity and labour income of 3.8 M working hours and €391 M, respectively.

TOWARDS THE FUTURE



- **Selecting patients that benefit** – While immuno- and targeted therapies improved the lives of many melanoma patients, high unmet needs remain for a subset of patients. Improved diagnostics will enable better selection of patient groups that will benefit from immunotherapies and/ or targeted therapies. Melanoma patients who will not benefit from immunotherapies and targeted therapies therefore will not be at risk of developing unnecessary side effects.

Melanoma is a growing public health concern and the most dangerous type of skin cancer, representing 4% of all skin cancers and 80% of skin cancer deaths



Melanoma



In 2020, over **106,000 patients were diagnosed with melanoma** in EU27¹. The incidence of melanoma has steadily increased over the past decades¹ and is expected to continue to grow with another 13.7% by 2040, to nearly 121,000 diagnoses per year



Melanoma is the **6th most frequently occurring cancer** in EU27¹



Melanoma occurs in **older and younger people**¹

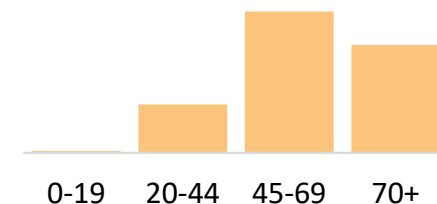


Melanoma is the **most dangerous type of skin cancer**. It represents only 4% of all skin cancer case, but 80% of all skin cancer deaths in Europe³

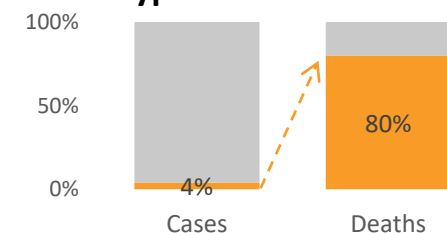


In 2020, **nearly 16,000 people died from melanoma** in EU27¹

Estimated distribution of age at diagnosis¹



Melanoma is the **most dangerous type of skin cancer**³

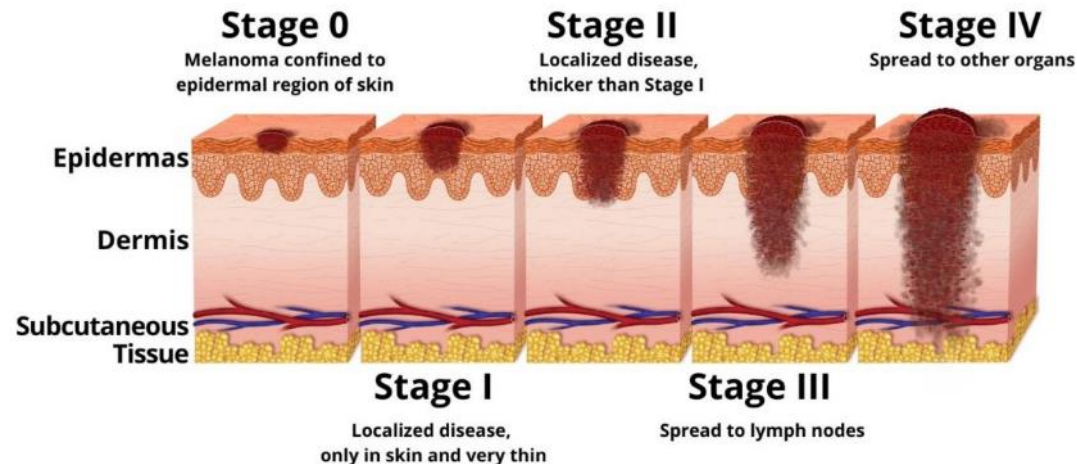


Melanoma: 4% of all skin cancer cases but 80% of skin cancer deaths

1. EUROPEAN UNION, 2021
2. EUROPEAN COMMISSION 2022
3. ESMO MELANOMA ESSENTIALS FOR CLINICIANS CHAPTER 1

Disease severity greatly depends on the stage of the disease, with a high unmet need for stage III and IV patients: no treatment available before 2011

Stages of melanoma¹



“There is no doubt that ten years ago we were not able to treat stage IV melanoma. We had 7-8% 5-year survival, for stage IV. It was horrible.”

– Dermato-oncologist and professor of cutaneous oncology

Stages of melanoma



There are **five stage of melanoma (0–IV)**, each divided in up to four subgroups (a–d) that indicate a higher risk within each stage

Stages 0–II²



Stages 0–II are typically **treated with wide excision** (surgery to remove the melanoma and a margin of normal skin around it)

Stages III and IV²



Stage III / IV melanoma (unresectable or metastatic melanoma) patients had a poor prognosis. **No scientifically proven effective treatment for stage III / IV** was available before 2011³

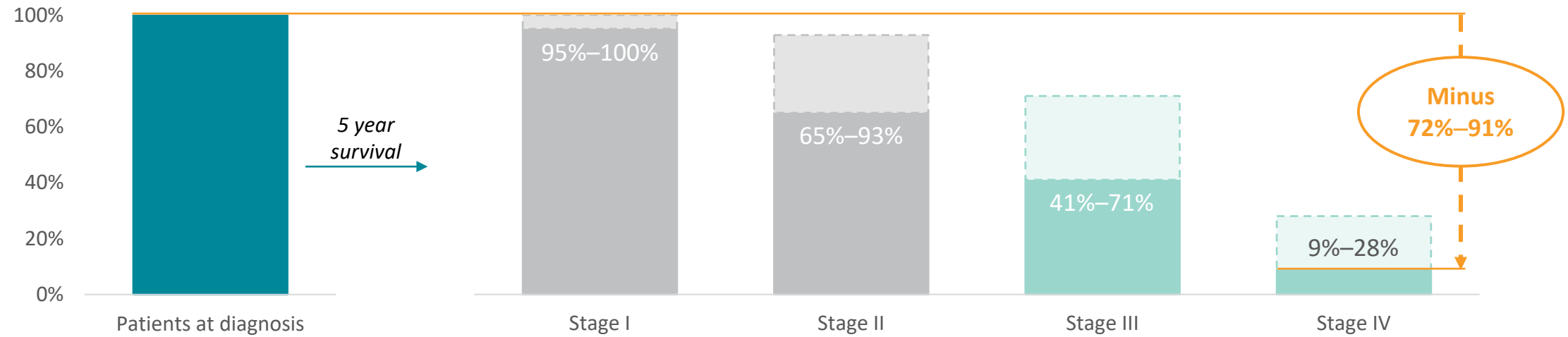
“With many other cancers, you could always hope that there would be something there that would treat it. But with melanoma, up until 2011, there was absolutely nothing.”

– Gillian Nuttal, CEO Melanoma UK

1. [HTTPS://WWW.AIMATMELANOMA.ORG/STAGES-OF-MELANOMA/](https://www.aimatmelanoma.org/stages-of-melanoma/)
2. AMERICAN CANCER SOCIETY, ACCESSED AUGUST 2022
3. INTERVIEW WITH HEALTHCARE PROFESSIONAL

Without effective treatment, late stage melanoma survival rates are extremely low. Only 1–3 out of 10 stage IV patients survived 5 years after diagnosis pre 2011

5-year survival rate before introduction of immuno- and targeted therapies¹



Stage III and IV melanoma **severely impacted** the **lives of patients** and their **friends and family**, as chances of survival were slim and no treatment was available

“Back then, certainly in the UK, we had absolutely nothing that treated melanoma. All that a patient would be offered in a stage III / IV setting would be radiotherapy or the old fashion chemotherapies. But clinicians and patients knew it was relatively unsuccessful in melanoma. A patient would have a 3-9 months life expectancy, which was a real tough situation to face for people. [...] From a patient point of view, it was absolutely such a blow to have nothing that could treat it [melanoma].”

– Gillian Nuttal, CEO Melanoma UK

We estimate that, in 2020, around 15.7k patients were newly diagnosed with stage III or IV melanoma in EU27

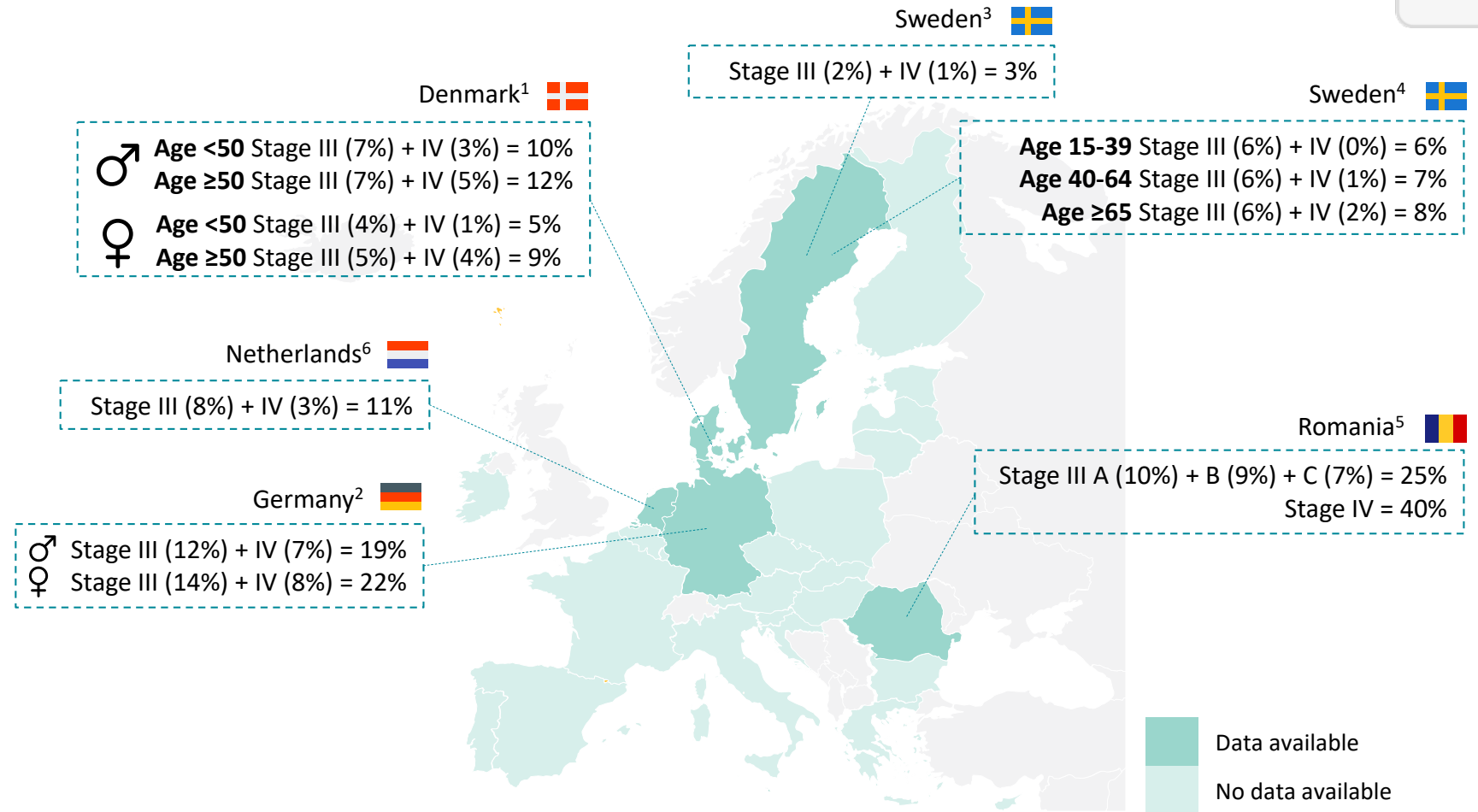
Distribution of patients amongst the various stages varies by country. This is due to the variety in screening and diagnosis. If countries focus on early diagnosis, relatively more patients are diagnosed in the early stages of the disease, preventing progression into later stages.

Information about the distribution of patients amongst stages is available only for a limited number of countries.

On the basis of studies from these countries, the average distribution of patients is:

- Stage III: **9% of patients**
- Stage IV: **6% of patients**

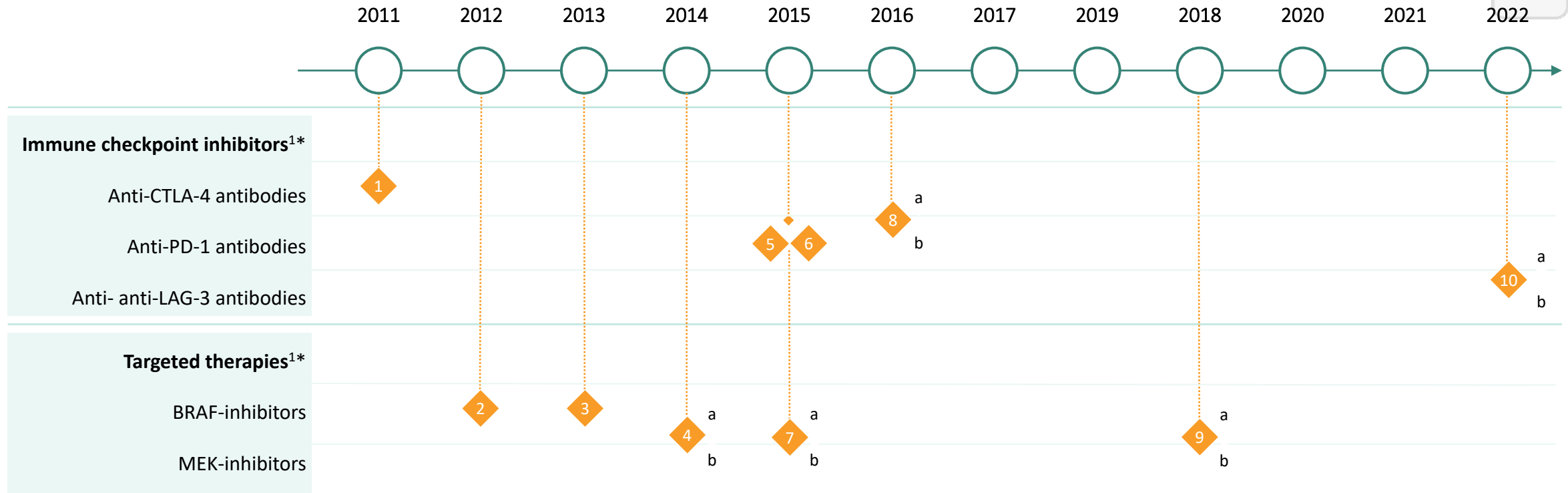
Unmet need for
~15,700 new patients per year



Countries where information is available about the distribution of patients amongst the various disease stages

1. BAY ET AL. 2015
 2. EISEMANN ET AL. 2012
 3. ERIKSSON ET AL. 2013
 4. PLYM ET AL. 2014
 5. ROTARU ET AL. 2019
 6. LEENEMAN ET AL. 2021

In 2011, the outlook for stage III and IV patients completely changed, with the introduction of several immuno- and targeted therapies*



“The dominant conversation in my clinic was about palliative care. That is what I was talking about to most patients. [...] And today, I’m in a situation to talk to people about Standard of Care options, which represent therapies with high level of benefit.”

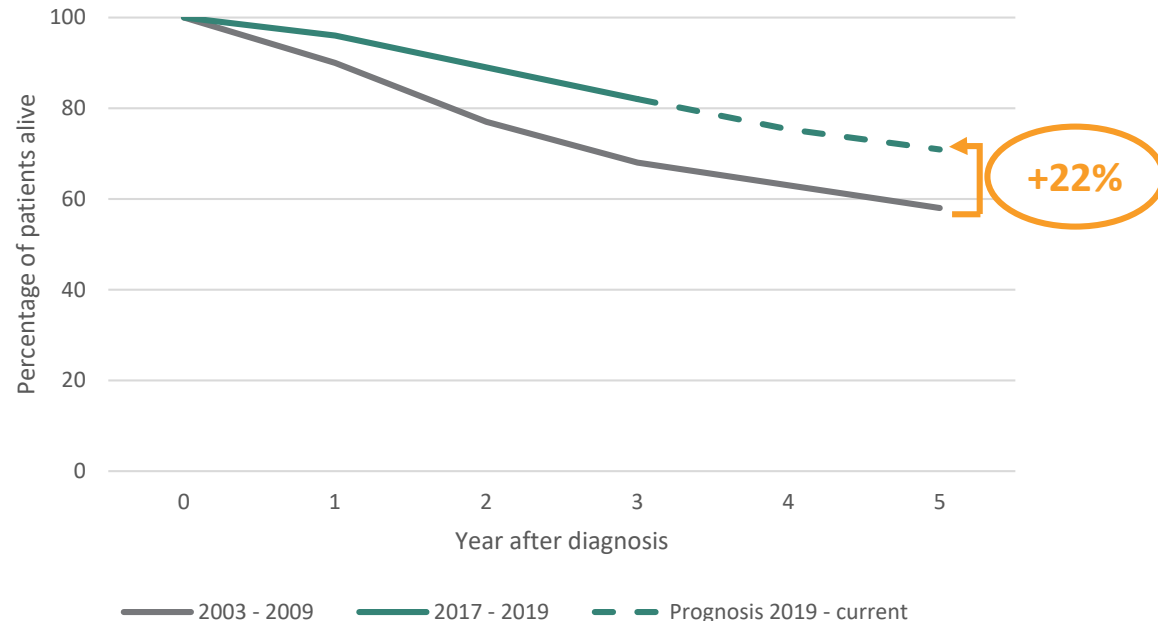
– Medical Oncologist and Cancer Researcher

* A / B INDICATE COMBINATION THERAPIES
 1. EUROPEAN MEDICINES AGENCY, ACCESSED AUGUST 2022

In the Netherlands, 5-year survival rates for stage III and IV melanoma have increased by 22% and 120%, respectively

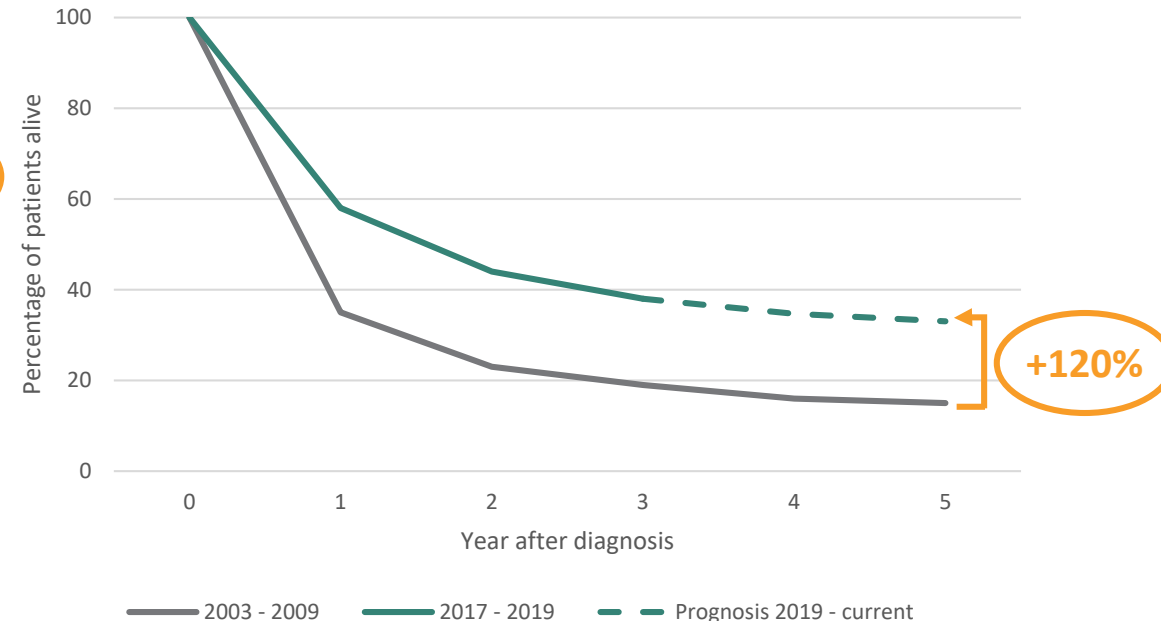
Stage III melanoma

The 5-year survival rate for stage III melanoma patients increased from 58% between 2003 and 2009 to 71% between 2019 and now¹



Stage IV melanoma

The 5-year survival rate for stage IV melanoma patients increased from 15% between 2003 and 2009 to 33% between 2019 and now¹



2368 more patients, of the 15.7k with stage III/IV, could be alive 5 years after their diagnosis if they are treated with immuno- and targeted therapies*

World without immuno- and targeted therapy for melanoma
(number of patients who are alive 5 years after diagnosis)**



World with immuno- and targeted therapy for melanoma
(number of patients who are alive 5 years after diagnosis)*



“In the course of 15 years, melanoma has evolved into being one of the most treatable metastatic cancers, today. That’s astonishing.”
– Medical Oncologist and Cancer Researcher

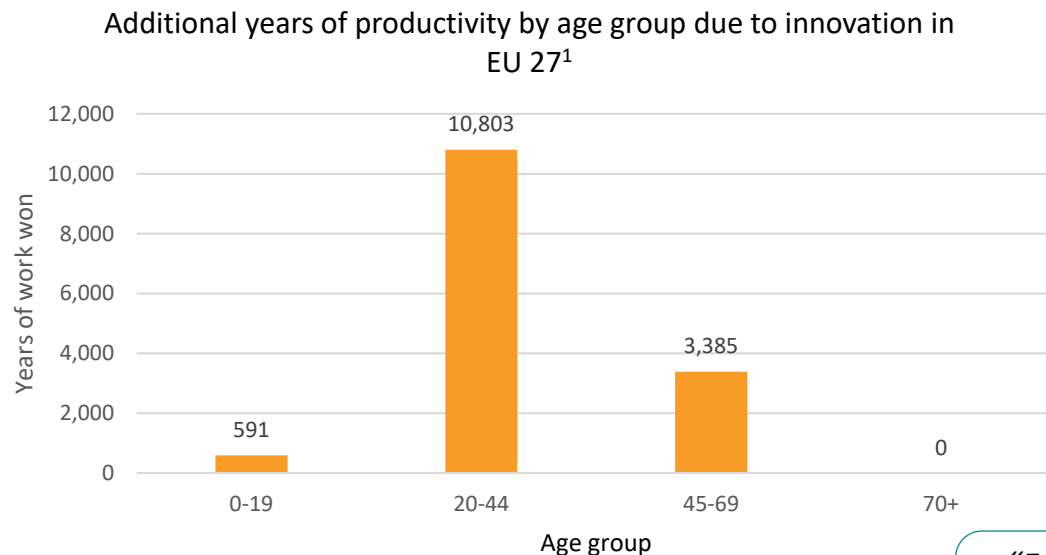
When patients achieve 5-year survival, their prognosis is good and relatively few patients die after 5 years. Treatment with immuno- and targeted therapies results in **an additional 2,368 patients being alive after 5 years*****

* ASSUMING THAT THE IMPROVED SURVIVAL RATES ARE ENTIRELY ATTRIBUTABLE TO IMMUNO- AND TARGETED THERAPIES
** CALCULATION ARE BASED ON A PROJECTION OF DUTCH SURVIVAL RATES ON EU27 INCIDENCE
*** DUE TO THE RELATIVELY YOUNG AGE OF THE INNOVATION, THIS CANNOT YET BE CURED PATIENTS YET

Improved work productivity due to the increase in survival rates for stage III and IV melanoma translates to 3.8M working hours and €391M income per year

Increased survival leads to increased work productivity

Stage III and IV melanoma patients who reach 5-year survival usually resume or continue work. The number of years of work left depends on the patient's age



Improved work productivity results in economic gain
Improved work productivity due to the increase in survival rates for stage III and IV melanoma results in:



Annual productivity in EU27 by^{1,2}
+ 3.8M working hours



Annual labour income in EU27^{1,2,3}
+ €391M

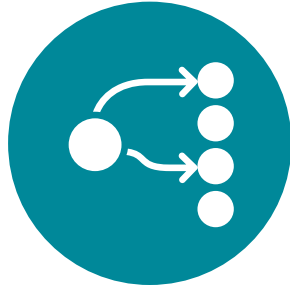
“From a societal point of view, we lost the ability for that man [a relative that died from melanoma] to earn and to pay taxes.”

– Gillian Nuttal, CEO Melanoma UK

1. EUROSTAT, UNEMPLOYMENT RATE. ACCESSED: AUGUST 2022
2. EUROSTAT, AVERAGE WORKING HOURS. ACCESSED: AUGUST 2022
3. EUROSTAT, ANNUAL EARNINGS. ACCESSED: AUGUST 2022

While immuno- and targeted therapies improved the lives of many melanoma patients, high unmet need remains for a subset of patients

High unmet needs remain for patients who do not respond well to current treatment. This can be improved by focusing on:



Improved treatment selection to increase efficacy

Via molecular diagnostics, to better match patient to treatment to improve efficacy¹



Improved understanding of tolerability

Via molecular diagnostics, to better understand the risk of adverse events by treatment²

"[...] we give the immunotherapy agents to all comers. Roughly 50% of these patients will have long-term survival. We have no means to predict in advance who that 50% of patients will be."

– Medical Oncologist and Cancer Researcher

Assumptions for the Melanoma case study



Distribution of patients amongst the various stages

- We based the distribution of patients amongst the various stages in EU27 on figures from Sweden, Denmark, Germany, Romania and the Netherlands. We calculated the (non-weighted) average from these countries. We assumed that the proportion of stage III and IV patients is the same for all age classes.

Survival rates and additional patients being alive after 5 years

- Survival rates were based on data from the Netherlands
- Survival rates for 2019 to 2022 are not available yet. For these years, we have estimated the survival rates by extrapolating the trendline from the most recent available cohort (2010–2016) to the cohort of 2017–2019
- We are aware that other factors, like better screening, could have influenced the improvement in survival rates over the past years. However, we cannot single out the impact of each intervention that took place between 2011 (when the first new agent was approved by the EMA) and now. That is why we assume that the improved survival rates are entirely attributable to immuno- and targeted therapies
- To quantify the additional number of patients being alive after 5 years, we applied the difference of survival rates in the Netherlands to the incidence and stage distribution in EU27

Economic gains

- We based these calculations on the additional 2,368 patients surviving 5-years after diagnoses
- We assumed that the mean hours of work in EU27 was the same for all age groups, for which we used 37.2 hours (2022)¹
- We assumed that mean annual earnings in EU27 were the same for all age groups for, which we used €27,081 (2014, most recent available year)²
- We corrected for the mean unemployment rate in EU27, for which we used 6.2% (2022)³
- We assumed that every patient would work up and until the age of 65

1. EUROSTAT. ACCESSED: JULY 2022. LINK: [HTTP://APPSO.EUROSTAT.EC.EUROPA.EU/NUI/SUBMITVIEWTABLEACTION.DO3](http://appsso.eurostat.ec.europa.eu/nui/submitviewtableaction.do3)

2. EUROSTAT. ACCESSED: JULY 2022. LINK: [HTTPS://EC.EUROPA.EU/EUROSTAT/DATABROWSER/VIEW/EARN_SES_ANNUAL_CUSTOM_3021783/DEFAULT/TABLE?LANG=EN](https://ec.europa.eu/eurostat/databrowser/view/EARN_SES_ANNUAL_CUSTOM_3021783/DEFAULT/TABLE?LANG=EN)

3. EUROSTAT. DATE: 3 MAY 2022. LINK: [HTTPS://EC.EUROPA.EU/EUROSTAT/DOCUMENTS/2995521/14613608/3-03052022-AP-EN.PDF/36631A07-778C-EF80-01F2-8A052BDE985E?T=1651561306689#:~:TEXT=IN%20MARCH%202022%2C%20THE%20EURO,FROM%207.5%25%20IN%20MARCH%202021.2](https://ec.europa.eu/eurostat/documents/2995521/14613608/3-03052022-AP-EN.PDF/36631A07-778C-EF80-01F2-8A052BDE985E?T=1651561306689#:~:TEXT=IN%20MARCH%202022%2C%20THE%20EURO,FROM%207.5%25%20IN%20MARCH%202021.2)

Full reference list

Research articles

- Bay *et al.* Incidence and survival in patients with cutaneous melanoma by morphology, anatomical site and TNM stage: A Danish Population-based Register Study 1989–2011. *Cancer Epidemiol* 2015; **39**(1):1-7.
- Craig & Virós. New biomarkers improve stratification of patients with melanoma. *Br J Dermatol* 2020; **182**(1):5-6.
- Eisemann, *et al.* Up-to-date results on survival of patients with melanoma in Germany. *Br J Dermatol* 2012; **167**(3):606–612.
- Eriksson *et al.* Low level of education is associated with later stage at diagnosis and reduced survival in cutaneous malignant melanoma: a nationwide population-based study in Sweden. *Eur J Cancer* 2013; **49**(12):2705–2716.
- Leeneman *et al.* Stage-specific trends in incidence and survival of cutaneous melanoma in the Netherlands (2003-2018): A nationwide population-based study. *Eur J Cancer* 2021; **154**:111-119.
- Plym *et al.* Clinical characteristics, management and survival in young adults diagnosed with malignant melanoma: a population-based cohort study. *Acta Oncol* 2014; **53**(5):688–696.
- Rotaru *at al.* A 10-year retrospective study of melanoma stage at diagnosis in the academic emergency hospital of Sibiu county. *Oncol Lett* 2019; **17**(5):4145-4148.
- Svedman *et al.* Stage-specific survival and recurrence in patients with cutaneous malignant melanoma in Europe – a systematic review of the literature. *Clin Epidemiol* 2016; **8**:109-122.

Reports

- European union, 2021: https://ecis.jrc.ec.europa.eu/pdf/factsheets/Melanoma_cancer_en.pdf

Website sites

- American Cancer Society, Treatment of Melanoma Skin Cancer, by Stage. <https://www.cancer.org/cancer/melanoma-skin-cancer/treating/by-stage.html> Accessed August 2022
- Cherry 2020, More for Melanoma: Nurse Discusses Unmet Needs. <https://www.oncnursingnews.com/view/more-for-melanoma-nurse-discusses-unmet-needs> Accessed August 2022
- ESMO Melanoma Essentials For Clinicians Chapter 1. <https://oncologypro.esmo.org/education-library/essentials-for-clinicians/melanoma-other-skin-cancers/chap-1-epidemiology-prevention-screening-and-surveillance> Accessed August 2022
- European Medicines Agency. https://www.ema.europa.eu/en/medicines?search_api_views_fulltext=melanoma Accessed August 2022
- IKN , melanoma 5-year survival (2003–2019). <https://iknl.nl/nkr-cijfers> Accessed August 2022
- Eurostat, unemployment rate. <https://ec.europa.eu/eurostat/documents/2995521/14613608/3-03052022-AP-EN.pdf/36631a07-778c-efb0-01f2-8a052bde985e?t=1651561306689#:~:text=In%20March%202022%2C%20the%20euro,from%207.5%25%20in%20March%202021> Accessed August 2022
- Eurostat, average working hours. <http://appsso.eurostat.ec.europa.eu/nui/submitViewTableAction.do> Accessed August 2022
- Eurostat. Annual earnings. https://ec.europa.eu/eurostat/databrowser/view/EARN_SES_ANNUAL_custom_3021783/default/table?lang=en Accessed August 2022

Interviews

Interviews conducted in July and August 2022 with 1 Patient Expert and 2 Healthcare Professionals (KOLs).



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